

recent realization of the ubiquity of cirrhosis exemplifies, and until the problem has been more specifically examined it cannot be said that ulcer does not occur in the more primitive races. The proponents of the civilization theory usually indict the "increasing pace" of modern life but do not say in what way stress and strain is greater than it was a century ago. We are entitled to ask those who make these glib assumptions to indicate what particular factors they hold responsible. These are not immediately evident. Civilization may even expose us to poisons from which primitive races are exempt, e.g., the toxic bleaching agents of white flour. If it is true that these are responsible for some forms of canine hysteria, it is not impossible to conceive of some toxin, regularly ingested, as a factor in ulcer formation.

INTRA-GASTRIC FACTORS

The experimental work on the production of ulcers in animals and the clinical observations on ulcer in man provide a welter of facts from which it is possible to deduce certain conclusions. Ulcer occurs only in those sites to which acid and pepsin have access, i.e., the lower end of the œsophagus, the stomach, the duodenum, the small intestine anastomosed to the stomach, and the intestine adjacent to a Meckel's diverticulum containing gastric mucosa. Well-documented cases of ulcer with achlorhydria are practically unknown and ulcer has never been known to occur with pernicious anæmia. These facts prove that the acid-pepsin factor is an essential one. Of these two, the acidity has been far more widely studied, not because it is more important but because it is more easily estimated. In what respect then, if any, does the secretion of ulcer patients differ from that of normals?

Recently, Ihre (1939) has carefully studied human gastric secretion using a histamine and an insulin stimulus. From his work it appears that in gastric ulcer cases the rate of secretion is within normal limits, whilst it is definitely increased in cases of duodenal ulcer. With regard to concentration of acid, higher acidity than normal was never encountered, about half of the duodenal cases showing values equal to the highest in the normal series, whereas this was a rare finding in the gastric ulcer series. The concept of hyperacidity, in the precise meaning of the term, is therefore without any experimental foundation, but the total output of acid in the cases of duodenal ulcer is greater than normal. Ihre also carefully studied the pepsin values of gastric juice and showed that in chronic ulcers the concentration and output of pepsin may be increased, particularly in the duodenal series. The difference from the normal may be very marked indeed and it seems that the importance of pepsin concentration and output has been overlooked.

The experimental evidence indicating the acid pepsin factor is entirely convincing (Wangensteen, 1945). Injections of histamine in beeswax, which produce a continuous secretion of acid juice never free from pepsin, produce a very high percentage of ulcers in nearly all animals in which it has been used. Starved rats even develop gastric erosions in a matter of hours if the pylorus be tied with a cotton thread so that unneutralized juice is retained in the stomach.

incidence of dyspepsia among those persons who had been subject to anxiety of mind, a state he evidently found less common in the lower social classes as "the nature of their engagements does not subject them to those embarrassments which bear down the energies and prostrate the mental powers of those engaged in the turmoil of mercantile or professional life". He also noted that "the effect of anxiety appears to be the production of acidity".

Since then, many investigations to correlate physiological change with mental state have been made and, following such clinical observations as those of Davies and Wilson (1939), it is now usually assumed that anxiety is an important factor in the genesis of ulcer. Anxiety is assumed to act through a nervous pathway by stimulating gastric activity and secretion. The assumption is implicit in this reasoning that certain emotional states are always correlated with certain altered changes in gastric function.

All investigators who have tried to correlate facial expression with an emotional situation have failed to find any close correlation whatsoever, and this is in accord with everyday experience. There may be great difficulty in determining the emotional attitude of a stranger from watching his face. Laughter usually denotes a friendly attitude but may often conceal embarrassment or even denote annoyance; some people pale, some flush with anger. If the facial expression is so poor an indicator of the emotional feelings of a person, will gastric function correspond more closely?

Wittkower (1935) found an absence of any fixed gastric response to the same emotion in different people, nor was there a different response to different stimuli in the same person. Todd found that medical students reacted to anxiety in different ways. In most, inhibition of motility was produced, but in some hypermotility occurred. Wolf and Wolff (1944), in their detailed studies of their subject Tom, noted two types of gastric functioning: a depression of acid output, motor activity and vascularity and an acceleration of these functions. They thought the first response corresponded to a reaction of withdrawal and the second denoted unfulfilled aggressive desires.

Thus, although it is true to say that an emotional situation can profoundly alter the function of the stomach, there is no immediate means of telling the particular response of the individual. And if the particular individual reacts to continued anxiety with depression of gastric function, this would seem to act as an insurance against ulcer.

HORMONAL FACTORS

So far I have dealt with the nervous phase of gastric secretion; about the hormonal much less is known. There can be extracted from the pyloric mucosa a hormone, free from histamine, which stimulates gastric secretion in animals; this has been named gastrin. The conditions of its formation and secretion are still debatable but they are likely to attract considerable interest in the future, and may explain why the stimulation of an ulcer with gastric juice stimulates the formation of more secretion. The status of gastrin is of more than theoretical interest, as if it plays an important part it should be possible to render a stomach achlorhydric by cutting the vagus and re-

The main feature in which stomachs with peptic ulcer, particularly duodenal ulcer, differ from normals is in their continuous night secretion when the stomach is empty. Levin, Kirsner *et al.* (1948) found that in duodenal ulcers the output of free hydrochloric acid during the nocturnal secretion was approximately three and a half times as great as in normals. Periods of anacidity were common in the normal series and were exceedingly rare in the ulcer series. There is therefore both human and corroborative experimental work to emphasize the importance of a flow of gastric juice in the empty stomach. What stimuli produce this secretion?

Three phases of secretion are recognized: a nervous, produced by the sight or thought of food which utilizes the vagal pathway; a hormonal, due to the presence of food in the stomach and possibly the duodenum producing a circulating hormone; and a later phase, ill investigated, due to products of food digestion in the small intestine.

THE AUTONOMIC NERVOUS SYSTEM

Attention has long been attracted to the possibility of vagal overaction as a cause of continuous hypersecretion and thereby ulcer, and this interest has been renewed by the recent work on vagotomy.

Rokitansky (1842-44), noticing the association of gastric lesions with intracranial lesions, wrote: "The proximate cause may be looked for in a diseased innervation of the stomach, owing to a morbid condition of the vagus and to extreme acidification of the gastric juice".

This association of gastric ulcers with intracranial lesions interested Cushing (1932) and he described several cases in which the cause of the gastric ulcer was undoubtedly due to an intracranial lesion. Much work has been done to try to localize some centre in or near the hypothalamus affecting gastric motility and secretion, and this work has been summarized by Sheehan (1940).

He regards the evidence as strong for a centre in the lateral hypothalamic area regulating gastro-intestinal activity and evidence not so strong for the existence of a centre in the supra-optic area, stimulation of which produces increased secretion of gastric juice. In a large series of experiments, hæmorrhages and erosions occurred in about one-third of all cases of hypothalamic injury and much more frequently than with other injuries elsewhere in the central nervous system. The occurrence of erosions associated with changes in the midbrain and pontine areas he explains as probably due to involvement of descending pathways in the autonomic nervous system.

These anatomical studies, with the concept of autonomic dysfunction derived from von Bergmann, naturally lend support to the hypothesis that ulcer may arise ultimately from constant psychic tension producing change in autonomic balance.

The observation that altered states of mind can profoundly affect body function is as old as recorded history, but the first statistical attempt to relate anxiety to dyspepsia appears to have been made by Fenwick (1868), who noted an increased

in dogs with a type of gastro-jejunal anastomosis in which ulceration is otherwise regularly produced. This preventive action cannot be explained by the inhibitory effect on gastric function, and it would seem to indicate a specific effect on raising mucosal resistance. The extract has been used in the treatment of ulcer in man but its healing effect cannot yet be said to have been definitely proved.

Another line of inquiry resulted in finding in the urine a gastric inhibitor, which has been named "urogastrone".

Following the clinical observation that peptic ulcer is rare in pregnant women, extracts of their urine were made and tested for the presence of some ulcer-preventive substance. An extract was found which had this activity and which also inhibited the secretion of gastric juice and the motility of the stomach. The substance has since been found in the urine of males and non-pregnant females and reports have been made that the urine of ulcer patients is defective in this substance. The methods of biological assay, however, are so approximate that this conclusion cannot be regarded as proved.

The status of these still relatively crude extracts and their relation to the endocrine system generally is not established. The obvious conclusion is that urogastrone is simply enterogastrone excreted in the urine, but there is much evidence against this view. Exact proof must necessarily await the isolation and crystallization of these substances, but unfortunately their biochemical purification has proved exceedingly difficult.

Sandweiss (1945) has made the unconfirmed observation that ablation of the pituitary resulted in the urinary extract losing its inhibitory activity, and this may indicate that the pituitary gland is the source of the hormone, or that it or the nearby hypothalamus may stimulate another organ to secrete it. It also raises the possibility that the results of the experimental surgeons in producing peptic ulceration by stimulating certain parts of the brain may have quite another explanation from the usual neurological hypothesis deduced.

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secting that part of the stomach which forms the hormone, without removing any of the actual secreting cells.

The antagonist in the battle against peptic erosion is the resistance of the mucosa to digestion and, in the undue attention paid to the acid and pepsin factors, this has often been overlooked. Undoubtedly the first line of defence is the presence of mucus, and when the power of the mucosa to secrete mucus is lost, erosion may occur. This is clearly brought out by the experiments of Wolf and Wolff (1944), who were able to produce a typical chronic ulcer in a few days by exposing to the continuous action of gastric juice an area of mucosa exhausted of mucus secretion. Unfortunately, biochemical examination of mucus has been meagre owing to the difficulty in handling it, but it is possible that its resistant properties depend upon substances formed by the liver; to support this hypothesis there is some evidence of associated liver malfunction in cases of peptic ulcer.

Quite apart from the protective action of mucus, the gastric mucosa appears to possess a specific resistance to digestion. Price and Lee (1947) implanted various living tissues into the stomach and found that of them all, gastric mucosa was the most immune, and that once tissues so implanted are covered with proliferating gastric mucosa they appear to be safe from further corrosive action of gastric juice.

Apart from the natural resistance of the mucosa, there may be local vascular lesions weakening the integrity of the mucous membrane. Arterial spasm or embolus has been indicted and the importance of this vascular factor, long suggested, has considerable experimental proof.

Wangensteen (1945), who noted hæmatemesis following the fat embolism after fracture, tried the effect of injecting fat into rabbits previously shown to be resistant to histamine in beeswax alone. The combination of fat embolism and histamine in beeswax produced perforated ulcer within a few days in nearly all his rabbits. Ulcers were similarly produced by epinephrine and histamine, the results here being ascribed to the local areas of anæmia becoming susceptible to the digestive action of the gastric juice. Wangensteen also makes the interesting suggestion, again on the basis of careful experimental evidence, that the bleeding which may occur in cases of portal hypertension, and loosely ascribed to the rupture of a dilated vein, may really be due to erosion of a mucosa the resistance of which is weakened by venous stasis.

In recent years, the possibility of raising the resistance of the mucosa to digestion by the use of one of the *gastro-intestinal hormones* has arisen (Sandweiss, 1945). These hormones, elaborated in the wall of the gut, have a local and powerful action, upon which the gut largely depends for its autonomous working. Such hormones are "gastrin", the histamine-free extract of the pyloric mucosa which stimulates gastric secretion; "cholecystokinin", which stimulates the contraction of the gall-bladder; "secretin", stimulating pancreatic secretion; and, of recent years, "enterogastrone", an extract of the intestinal mucosa which inhibits gastric secretion and motility in animals and probably in man. In addition to its inhibitory activity, this extract has been shown to exert a surprising effect in preventing ulceration

neutralized, the peptic ulcerative process should be more under control. Some surgical authorities deprecate the present-day tendency to employ this comprehensive title, preferring to refer to gastric and duodenal ulceration as distinct and separate entities. It is true there are certain distinctions which call for differences in surgical approach and technique; and there is the possibility of malignant degeneration, which exists in the gastric and not in the duodenal ulcer. If ulcers are to be designated as either gastric or duodenal, a third, equally peptic, must also be added—the jejunal ulcer. This latter ulcer remains a solitary reminder of our ability to produce a true peptic ulcer by exposing the jejunum to the acid juice through surgery, an event which should always be a deterrent to premature interference.

During the last twenty-five years there have been considerable advances in the management of the patient with peptic ulcer. Gone are the days when debates were held comparing surgical with medical forms of treatment. Gone also are the days of wholesale extraction of teeth and other potential sources of sepsis. The ulcer patient has now become the subject of study more than the ulcer. Through these studies of the ulcer individual, he has been shown to be a not unworthy citizen. His zeal for work; his restless energy; his willingness to shoulder responsibilities; his intense desire to be well and “up and doing”, are features not shared by other chronic dyspeptics. Added to these features, there is also his ability to enjoy normal digestion for long periods at a time. His acute sense of smell and of taste, and his readiness and indeed eagerness to discuss food are properties of an individual with a healthy active secretion.

ENVIRONMENTAL FACTORS

The medical adviser must get to know his patient well. He should become familiar with his responsibilities; should know his home and his domestic anxieties, his job and his fears. It is true that when all is well with the ulcer individual, all is completely well. “Let digestion wait on appetite and health on both.” Once the situation of the ulcer has been recorded by radiology and a good history has been obtained of the severity of symptoms and of the number of recurrences, it is still necessary to probe deeper into the patient’s life and his environment. To remain unaware of a sudden increased responsibility or of some acute financial loss, and be content only to talk of powders and pills is, to say the least of it, touching only the fringe of the problem. Delving into the personal affairs of the individual can only be done sympathetically and with an obvious sincerity to help. Such probing must be done in strict privacy. If the patient be admitted to the publicity of a hospital ward where other patients are all around him, with nursing staff and students too, an iron curtain has already descended between him and his physician. The uprooting of personal events at such a time can only be done unkindly, and often without much success. In other words, the privacy of the home or of the consulting room, or of a small room away from the ward with none other present, is essential and proper. When

THE MEDICAL TREATMENT OF PEPTIC ULCER

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THE treatment of the patient with peptic ulcer is as much the treatment of the patient as that of the ulcer. It becomes an individual problem although the ulcer itself shows all the common characteristics. Treatment must be comprehensive, and not only the man but his surroundings and responsibilities must become known before we as medical men can hope to guide him and help to heal his affliction. Wherever our interest lies in our dealings with this very common disorder, whether we look at the problem in an individual way as the family doctor is expected to, or as the surgeon expert in modern surgical technique, or as the physician in a large hospital centre accustomed to weighing this and that form of therapy, there is a certain groundwork of knowledge which must permeate and dominate all our thoughts on how best to help and guide the patient. Therapy must depend in large measure upon what we believe and know. It is accepted that peptic ulcer is a benign and recurring disorder. Benign in that the mortality is low: benign in that the incidence of serious complications is not high, and benign in that the victim can most certainly grow out of his trouble and remain well. It is also known that peptic ulcer is a recurring disorder in that it is usual for patients to complain of attacks sometimes in the spring, sometimes in the autumn, and not infrequently following a mild respiratory infection. And as often as not the attack passes off without any determined form of treatment. That it recurs is well known: that it recurs following surgery even of a radical nature is less well appreciated. That the classical symptoms of pain after food and pain relieved by food but not accompanied by a demonstrable ulcer are often seen is again sometimes forgotten. It is also known that an ulcer can heal and not recur. Nature is a great healer, and she probably does so more often in the stomach than we have been inclined to believe in the past. Perhaps indeed, the reputation of many an extensive surgical procedure depends more upon this recuperative power inherent in the stomach than upon any other factor. Who knows? Sufficient is known therefore to attribute to peptic ulcer the distinction of being a benign although a recurring disorder. Moreover, it must be remembered that whatever form of treatment be employed spontaneous healing does occur; that symptoms can exist without an ulcer, and that as the patient grows into the ulcer age, so also he can grow out of it.

It is as well to keep the term "peptic ulcer" in mind, for it denotes the peptic origin of the ulceration. It emphasizes the part played by the acid-eroding juice. If the acid juice can be diminished in quantity, or constantly

sound maxim to masticate food to a soft pulp before swallowing. This is certainly true in the treatment of gastric ulcer. Provided the diet is frequent, that is, two-hourly or hourly if pain persists, and all solids are masticated into a soft pulp before swallowing, it is possible now to be less rigid than in years gone by in regarding what to eat and what not to eat. Milk obviously will remain an essential constituent of the diet, but emphasis to-day has centred more on the importance of giving a diet sufficient in calories and adequate in protein and in vitamins. Diet sheets, although serving a useful function, must be modified to suit the patient and his work. So obedient are some patients, so desirous of doing what the doctor ordered, that they will abstain from partaking of food if that food which is offered them is not included on their cherished diet list. And in consequence they commit the sin of omission which is probably more damaging than the sin of commission. Not to eat, and in consequence to allow the acid juice to bathe the mucosa in high concentration, can do nothing but harm. Mention has already been made of the highly developed sense of taste and smell in the man with peptic ulcer. It is impossible not to feel sorry for the ulcer patient in an ordinary hospital ward, when he is forced to partake of milk and milk products, and he sees his neighbours partaking of ordinary dinners and ordinary suppers. Such sight and smell of food stimulates further the production of acid juice. It is well to point out to him the importance of the last feed at night. Milk taken alone at ten o'clock at night may be out of the stomach within an hour or so. Bread and milk or biscuits and milk are more likely to remain a longer period and buffer the juice more thoroughly. He should always have milk at his bedside and should partake of this if awake, even though not in pain. In fact he should not lose any opportunity throughout the twenty-four hours of diluting and neutralizing his gastric juice. If he remains faithful to two-hourly feeds and masticates his food thoroughly he may lose his symptoms rapidly. He may also show a gain in weight and a progressive improvement may be recorded in the radiological appearance.

DRUGS

The practitioner will know that he can help further by adding to this simple regime medicaments of his own choice. If there is tension, and usually there is tension in the ulcer patient, a sedative taken regularly will help to allay the bombardment of the stomach. A measure of this alertness and quick reaction to environment can often be seen in the young ulcer individual by simply stroking the abdominal wall. How vigorous the abdominal reflexes are and how sometimes under our very eyes we can see vasomotor changes on the skin surface. A convenient sedative, and one I consider superior to phenobarbitone, is *amytal*: either $\frac{3}{4}$ of a grain (50 mg.) twice a day, or $\frac{1}{2}$ a grain (32 mg.) four times a day. It has been my custom to give such a preparation for a year or more. The experience gained suggests that it is capable of exerting material good. I have also found that patients while taking such a sedative regularly have been able to go through certain crises in their lives

this privacy is secured it is necessary to show, and if possible to convince, the patient that there is a connexion between that recent anxiety of his, that anxiety of uncertainty whether such and such can be accomplished, and his recent pains. He will need to know before he is convinced that there is an intimate and anatomical connexion between his nervous system and his stomach. He should also learn that the "acid" which the laity so often talk about is in fact increased in quantity during these periods, and that it is often poured out needlessly through the night as well as the day. Once such a patient sees and believes, he is far more solidly on the right road. He may remain unconvinced, and think that it is a tall story that anything can upset his stomach other than some food. How ready he is to believe that there is some mysterious elixir just round the corner: some powder or pill or injection that can dispel his dyspepsia into thin air!

If the patient can see clearly that there is in truth a direct relationship between his attack and a recent disturbance in his life, he may be able to be forewarned and forearmed in the future. Again, if as a result of such a talk, which may have to be oft repeated, on the importance of neutralizing the eroding juice, and the wisdom of buffering it with frequent feeds, if this also is understood it is far more likely that the irksome attention to detail will be faithfully followed. There has been a tendency in certain centres, where the emotional factor in ulcer has been appreciated, to advise psychological help. As we ask our surgical colleagues to deal with certain of our patients, so the physician might consider sending ulcer patients to a psychological department to inquire into their responsibilities, anxieties and fears. It would be indeed unfortunate if such a tendency became general. For the medical man who deals with the stomach is the only person to deal with the man and know all about him and his environment. Of all within the profession none can equal the family doctor, for he already knows a good deal of the family tree, much of the man himself, and sometimes a fair amount about his responsibilities and his reactions to them.

THE BASIS OF DIETARY TREATMENT

It is as well to point out to the patient that, since the acid juice is such an essential factor in the production of the peptic ulcer and that this acid juice is secreted at all times of the twenty-four hours, the more thoroughly he buffers his juice with bland food the more quickly will nature heal the eroded surface. It is also good to point out to him that this repaired tissue is friable and fragile, and that good work done over a period of three weeks with bland food and frequent feeds can be as easily undone within twenty-four hours by allowing the acid juice to rise in concentration through abstention from food, resulting in a return of the original crater.

The more complete the initial treatment, the more solid the healing and the less the liability to a breakdown. It is partial treatment with partial healing and repeated breakdowns that produces the fibrosis, the deformity and the eventual mechanical disability of obstruction. It has always been a

adjust his life and his responsibilities. Hospitalization, although necessary in some cases, does not offer every advantage. There is a lessened opportunity for privacy. He becomes a person dealt with by the many rather than by one; he may also be influenced to believe that hospitalization means a defined term of treatment, and once he is discharged from hospital, presumably cured, he can once more, being symptom-free, return to his old way and old customs. But if he is given good fortune and symptoms readily abate, it is possible to see radiological improvement, especially so in lesser curve ulcers, within the period of three to four weeks. The regime must of course be followed for at least a year, including two-hourly feeds.

Rest.—When the ulcer is causing considerable pain and the patient is disturbed at night, it is then necessary to secure him physical as well as mental rest. Hard manual work is difficult when pain is constant. When pain persists, even in spite of rest in bed combined with frequent feeds, it may be necessary to resort to a milk drip, especially at night if the nocturnal secretion is excessive. Gastric lavage twice a day, although there may not be any appreciable gastric delay, may also help such patients when the pain is severe. If surgery is deemed desirable, a preliminary period of rest, from four to six weeks, will improve the local state of affairs and make the patient more fit for operative treatment. Whether the patient be treated in an ambulatory fashion or by rest in his home or hospital, repeated radiological examinations are not only necessary, but in all probability they exert a good effect on the patient. Evidence of healing brings with it its own therapeutic reward in satisfaction and content. It is my custom to repeat this radiological inspection at the end of a month, and again in two or three months' time.

INDICATIONS FOR HOSPITALIZATION

Admission to hospital always becomes advisable in those showing some degree of *gastric retention*. This condition may appear quite suddenly in a patient who gives a long history of indigestion, precipitated often by some transient infection. The condition may show all degrees of severity. In the past this condition has perhaps been diagnosed too readily as pyloric stenosis. To those trained in pathology, pyloric stenosis is considered as permanent a state as mitral stenosis; but the response to non-surgical treatment is often so dramatic that until there is proof that there is permanent gastric delay it is better to use the term gastric retention rather than pyloric stenosis when the patient is first seen. In addition to showing clinical evidence of gastric delay discernible by palpation and auscultation of the abdomen, the patient may complain of vomiting, nausea and loss of appetite, and he may have made his condition worse by his own administration of alkali. Three to four weeks in bed with daily gastric lavage and rectal fluids to combat the dehydration will often produce a considerable change in the patient's appearance as well as in the local state. The tongue which was dry becomes moist; the signs of dehydration disappear; the nausea is replaced by a desire for food; the blood urea, which is often high, returns to normal; and the large bag of a stomach with barium retained for as long as

without suffering recurrences. Time has given *belladonna* an honoured place in the therapeutics of ulcer, and ten drops of the tincture prescribed twice or thrice daily has been a custom for some years. It certainly helps if there is much pyloric spasm, but it probably fails materially to alter the gastric secretion, and sometimes patients show signs of intolerance even on this small dose.

Alkalis are less in favour than they were. It was the custom in years gone by to give alkalis in large and frequent dosage, but it is now known that the alteration in gastric acidity is transient following their use, and there is some evidence that there is a rebound and an actual increase in acid secretion. On the other hand, there is abundant evidence that alkali does relieve pain, and as a walking stick can be used when lame, so if the patient knows from experience that such and such a powder does relieve him, there is little reason to condemn its use. But "living on alkali" cannot but be condemned. Whilst allowing its use, it is right and proper to explain that its effect is temporary and that if it be used sparingly or not at all, so much the better. Alkalosis was always a possibility in the years gone by. If it remains unrecognized it may cost the patient his life. It is necessary to be alert and aware of this possibility when seeing a patient who may give a history of much pain, who has been vomiting, who has taken a fair amount of alkali, and who shows the signs and symptoms of dehydration. With the mental symptoms that are induced it may indeed be forgotten and other morbid states thought of.

The disadvantages of the soluble alkalis have been overcome by the development of *non-absorbable antacids*: colloidal aluminium hydroxide or phosphate, and magnesium trisilicate. These preparations may not be so immediate in their relief-giving properties but as antacids, both in the laboratory and in clinical practice, they have proved their worth. Up to the present no deleterious action has been recorded with the use of trisilicate, but it appears that the aluminium antacid taken in large quantities may induce or increase any gastric delay. Provided antacids are used to relieve symptoms and not to replace frequent feeds, they can be safely retained in the peptic ulcer regime. Occasionally, when the ulcer is situated high up on the lesser curve of the stomach, a more viscid preparation appears to be more serviceable in relieving pain.

GENERAL MANAGEMENT

If the condition of the patient is assessed as being reasonably good, and he himself is found to be cooperative and sensible, it is quite feasible that healing of the ulcer may be secured while the patient remains at work. Much will of course depend upon the character of the work, the opportunities for frequent feeding, and the regular hours and type of employment. If this healing is acquired while continuing to work it is a greater gain, a victory won, and the patient is more likely to continue with this new regime and method of feeding. He is made to realize his dependence upon himself and that his relief from trouble has resulted from his own ability to re-

acid juice, and, while not going to the whole length of the Meulengracht diet, I have adopted much the same regime in the bleeding ulcer as in the non-bleeding ulcer: that is, frequent and two-hourly feeds of milk and milk products. Vitamin C, especially in those patients who have partaken of no vitamin C containing foods, has been advocated in big dosage. The vast majority of ulcer patients who are admitted for gastric hæmorrhage, fail to show an ulcer crater when they are investigated some three weeks after admission. In other words, healing has already occurred.

In dealings with dyspeptic individuals it must be admitted that in the past there has been a somewhat harsh discrimination between the individual who shows no ulcer but identical symptoms and he who is "fortunate" at that moment to show an ulcer crater. This latter being is regarded as suffering from a structural demonstrable abnormality needing medical care. The other, since he shows no radiological departure from normal at that precise moment, is often told to go his way, and that his trouble is functional. We are rightly shaken as medical men when we are called to such a patient at a later date, showing all the signs of hæmorrhage or perforation. Ulcers readily heal and as readily and quickly form. That we fail to demonstrate one does not mean that one was not there to be demonstrated three months previously or in a week's time. The man who complains of pain relieved by food and by alkali, whether he shows a breach in his mucosa or not, deserves the same attention and the same privileges as those given to all ulcer individuals.

INDICATIONS FOR SURGERY

We are often asked when we should advise surgical intervention. Here again it becomes a highly individual problem. Some patients are so keen on having done to them what was done to their fathers or their brothers, that no amount of care or influence will bring relief or content to their minds. These few, determined as they are towards surgery, will eventually receive it at some place or another. When the mechanical effect of fibrosis is there to see, its correction can only be accomplished by surgical measures. The stenosis of the pylorus and the hour-glass formation are the two best known. Also, if an ulcer remains unhealed in spite of the most thorough medical regime of three months' duration, since it becomes a source of potential danger and of fatality, surgery is well advised. It is also known that if an ulcer fails to heal it will cause increasing rather than decreasing symptoms, thereby further curtailing the ability of the man to fill his place in society. The incidence of neoplastic change in an ulcer remains a debatable point. It is not easy to assess with any accuracy how often this does occur. That it does occur there is no doubt. It must be known and proved that the ulcer originally did heal, otherwise there is no proof that it was initially benign. Also, after an interval of sufficient length, it must be shown that on this same site another ulcer occurred which eventually showed the characteristic features of a carcinoma. Few examples can fulfil these conditions. Nevertheless, it should always be remembered as a possibility, and be an added influence towards consultation with a surgeon. Repeated

twenty-four hours will be seen to be reduced to a quarter of its size and emptying in reasonably good time. The stomach's capacity to adjust its size and function can only be surpassed by the uterus in pregnancy. This state of gastric retention, and indeed of gastric failure, for it is a failure of function, needs better recognition. Its treatment is medical, even though it may be necessary at a later date to deal surgically with a fibrosed pylorus. To operate as soon as a diagnosis is made on a dilated, exhausted stomach can only court failure.

It was once a debatable point whether a patient suffering from *hæmatemesis* or *melæna* should be transferred from his home to the hospital. In those former days there was little more that could be done in hospital than at home. To-day the advantages offered within an institution outweigh all other considerations. *Hæmorrhage* is an alarm signal to the relatives as well as to the victim, and there is always the possibility of a further and possibly fatal *hæmorrhage*. Admission to a centre gives immediate confidence to the sorely tried patient, and before his discharge he can be properly assessed regarding his ulcer. *Hæmorrhage*, like perforation, often follows some disturbing event in the patient's life. To know what such an event was, to bring it to the light of day, may mean that it can be avoided in the future, or at least that in similar circumstances special care can be exercised, and more rigid dietary precautions adopted. To-day it has become an established rule to administer blood to patients if there has been an appreciable loss. This is sound policy and the reduction in mortality in hospitals has fully proved the rightness of this course. Young people stand losses of blood better than the elderly; in men over sixty, cardiovascular complications may easily follow upon the anæmic state, the result of *hæmorrhage*. Once the dehydration has been corrected, and the recorded *hæmoglobin* becomes a true indicator of the state of affairs, it can be regarded as a wise rule to transfuse all those with less than 40 per cent. *hæmoglobin*. If there is a recurrence, the patient who has been transfused is able to withstand the shock of a second *hæmorrhage*.

Although the patient before admission may have suffered the usual pain, it is not common to find pain persisting in hospital. We often hear from the patients that once the *hæmorrhage* occurs all discomfort and pain disappear. Occasionally, however, the pain persists, and this combination of *hæmorrhage* and persisting pain, in my experience, bespeaks great danger. It suggests that there is active erosion proceeding possibly into extra-gastric structures, and that at any moment a *hæmorrhage* of too great a magnitude to control will occur. In a study of my cases I have come to the conclusion that in future, when pain persists into the third or fourth day following a *hæmorrhage*, surgical intervention will probably be a wise procedure, although the *hæmorrhage* might have been the first and the initial symptom. It is important that dehydration be corrected, and this can be done either by rectal or by intravenous fluids. Meulengracht has advocated a more liberal diet and has shown that there is a resultant reduction in mortality. Certainly if there is active secretion it is illogical not to buffer the

acid juice, and, while not going to the whole length of the Meulengracht diet, I have adopted much the same regime in the bleeding ulcer as in the non-bleeding ulcer: that is, frequent and two-hourly feeds of milk and milk products. Vitamin C, especially in those patients who have partaken of no vitamin C containing foods, has been advocated in big dosage. The vast majority of ulcer patients who are admitted for gastric hæmorrhage, fail to show an ulcer crater when they are investigated some three weeks after admission. In other words, healing has already occurred.

In dealings with dyspeptic individuals it must be admitted that in the past there has been a somewhat harsh discrimination between the individual who shows no ulcer but identical symptoms and he who is "fortunate" at that moment to show an ulcer crater. This latter being is regarded as suffering from a structural demonstrable abnormality needing medical care. The other, since he shows no radiological departure from normal at that precise moment, is often told to go his way, and that his trouble is functional. We are rightly shaken as medical men when we are called to such a patient at a later date, showing all the signs of hæmorrhage or perforation. Ulcers readily heal and as readily and quickly form. That we fail to demonstrate one does not mean that one was not there to be demonstrated three months previously or in a week's time. The man who complains of pain relieved by food and by alkali, whether he shows a breach in his mucosa or not, deserves the same attention and the same privileges as those given to all ulcer individuals.

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hæmorrhage associated with a chronic fibrotic ulcer, either in the duodenum or the stomach, is another indication. Severe pain, especially when associated with pain in the back, denotes an eroding and probably a fixed ulcer: one that is unlikely to heal with medical measures and one also that may task the resources of the surgeon on operation. On the other hand, size is no good criterion. Some ulcers remain radiologically small but at the same time have produced the most intense fibrosis. These need surgery. Others, very large in size, often show the most rapid healing, and the patient enjoys freedom from further trouble.

RECENT FORMS OF TREATMENT

Since it is known that spontaneous healing does occur, it is necessary to be forever cautious in appraising any new form of therapy. Enough is known about the influence of the nervous system with the vagal bombardment producing, for all to see, the demonstrable vascular and secretory changes in the gastric mucosa. Any therapy which does not include this dominant rôle must be assessed with certain doubt. The injection of sterile water can coincide with the natural process of healing, but we would be very disinclined to give credit to the water itself. Vitamin deficiencies have been observed in certain ulcer individuals in whom dietetic restrictions have been carried on for a long period of time. In consequence, certain of the vitamins have from time to time been applauded as necessary in preventing ulcer formation, and in healing existing ulcers. Similarly, injections of histidine no longer enjoy the support of medical opinion. More recently, extracts from the gastro-intestinal tract (enterogastrone and urogastrone) have been tried in the experimental animal and in clinical trials. Recent observations in this country and in America throw doubt on their efficiency.

There is some evidence that following vagal resection patients become less aware of their ulcers, and there is also sometimes a diarrhœa which is difficult to control. It is necessary to wait and see whether the results of cases already done will justify placing this operation among routine surgical procedures. It is hoped that our surgical colleagues will recall the enthusiasm of early days when a gastro-enterostomy was regarded as the one method of dealing with peptic ulcer, an enthusiasm that brought little credit to surgery and many a jejunal ulcer to the victims. On the other hand, the established partial gastrectomy has undoubtedly relieved many a resistant ulcer and enabled the patient to return to work and life.

CONCLUSION

The management of an ulcer individual is, and will always remain, personal. The best results are only obtained when the patient and his doctor are in full accord after a pooling of information, personal from the patient to the doctor and informative from the doctor to the patient, possibly resulting in an adjustment here and an alteration there. In no organ of the body is the repair process better seen, and no patient is more grateful and appreciative of help than the ulcer victim.

DIET IN PEPTIC ULCER

By E. MEULENGRACHT, M.D.

Professor of Clinical Medicine, University of Copenhagen.

THE medical treatment of peptic ulcer has two different immediate objectives:—(1) the dyspeptic disturbances, particularly the pains, and (2) the hæmorrhages, with the condition resulting therefrom. In both cases the question of the diet is paramount. In the first, it must contribute towards curing the dyspepsia, especially the pains; in the second, it must not increase the bleeding, but help to allay the post-hæmorrhagic shock and to aid convalescence. The ultimate goal in both is, of course, the healing of the ulcer.

In the past great reliance has been placed on a careful planning of the ulcer patient's diet, linked with subtle methods of cooking and careful dieting. In my opinion this has been wrong, for it is not the vital point. A patient does not develop an ulcer through eating. Ulcer patients are not a group of greedy individuals, to be punished because they have indulged too freely in the pleasures of the table. Peptic ulcer is acquired far more readily by not eating enough. Ulcer patients are much more accurately described as "starvers", as restless, extremely active persons who eat too little, not often enough, and who bolt their food. It is important to keep these facts in view when planning the diet of an ulcer patient.

TREATMENT OF THE PAINFUL ULCER

The basis of ulcer dyspepsia is the pain—the "cardialgia". This is due apparently to increased tone or spasm of the gastric muscles. It often occurs in the form of hunger pains before meals or as nocturnal pains. This is important because it does not indicate starving the patient. It is my view that much harm has been done to ulcer patients by starving them. The more severe the pain, the more they have been denied food; and this despite the fact that they often say themselves, "but I feel I want to eat".

Fresh ideas are gradually coming to the fore and new principles of treatment are beginning to be put in practice. Personally, I now use, and feel confident in recommending, the following rules for the medical treatment of painful gastric ulcer:—

- (1) Rest and relaxation.
- (2) A gradually increasing ulcer diet, adequate qualitatively and quantitatively, with frequent meals.
- (3) Alkali and belladonna.
- (4) No smoking.

Rest and relaxation.—There can be no doubt that the nervous element plays a predominant part in the development and persistence of peptic ulcer. The patients possess a particular nervous constitution ("ulcer

constitution"), they belong to the energetic, restless type, which has been accentuated in a large proportion of them by the incidents of everyday life: a forced tempo, anxiety and restlessness, sorrow and care. No one has pointed this out more convincingly than Davies and Wilson. Therefore rest and relaxation ought to constitute an important, perhaps the most important, factor in the treatment, with freedom from mental strain. This object is usually best attained by hospital treatment, and if it is possible I would regard a month's respite from work and home, with peace and rest in a hospital bed, as helpful or even essential, if an ulcer cure is to be carried out. I do not deny that a successful cure can be undertaken in the case of an ambulant patient; but it depends upon the circumstances.

Diet.—It is, to my mind, inexpedient, indeed impracticable, to prescribe a dietetic cure for ulcer which can be valid for all times and all places. Ulcer cure must depend upon circumstances and on the customary diet of the particular country and of the particular locality in that country. It must also be regulated partly by the individual status. But it may be taken as a basic principle that it is advantageous to begin with a soft, non-irritating, semi-fluid diet, and then gradually to increase it by the addition of more and more courses, so as to arrive at the end of a month at a varied and suitable diet that can be maintained without causing the patient or the domestic staff great inconvenience. As basic items in the diet, milk and eggs must be recommended, especially milk if it can be obtained. But as the cure progresses, the diet can also be built up with all other kinds of soft, non-irritating food.

The diet should be sufficient qualitatively, that is to say, it must contain the same amount of protective food as the ordinary diet, preferably more. If this is impossible, a mixture of the different vitamins may be added to meet the requirements. The diet must also be adequate quantitatively. The patient must realize that he is to eat heartily. A patient on an ulcer cure must put on weight.

Now we come to what is, without doubt, the most important point of all in the diet: *the frequent meals*. The principle has attained its most logical form in the Sippy cure with its requirement of meals every two hours. In my opinion the Sippy cure is too one-sided in its choice of food. I give a far more varied diet, but I endeavour to lay the greatest weight on the rule: a meal every two hours, though not during the night. Naturally every meal cannot be a large one.

As stated, I have personally persevered with the gradually increasing ulcer diet; it works well and at all events it has certain pedagogic advantages and the appearance of being part of the treatment. But it is possible that it might be just as well to begin with a freer diet, provided that the rest in bed and freedom from worry and so on are adhered to. My colleague, Professor Gram, adopts this method and, so far as can be seen, with equally good results.

Drugs.—I use the following mixture:—

Sodium bicarbonate.....	47 per cent.
Magnesium subcarbonate	47 per cent.
Milk sugar.....	3 per cent.
Extract of hyoscyamus.....	3 per cent.
One teaspoonful thrice daily	

I have been accustomed to prescribing this mixture to be taken at 9 a.m., 3 p.m. and 9 p.m., partly in the hope that the last dose will counteract any possible nocturnal pain that may arise. If there is nocturnal pain the patient must take an extra teaspoonful or eat a little "night food". At times the powder causes inconvenience in the form of slight griping and diarrhœa, or diminished power of accommodation and dryness of the mouth. In such cases the dose must be reduced. Pharmacologists point out that the powder is not quite suitable in that sodium bicarbonate causes after-secretion. But whether one sort of powder or another be used, or a special kind of tablet, does not seem to me of great consequence. Usually every country has its favourite compound, but the principle is the same: an acid neutralizing substance and some belladonna. The usefulness of these drugs has been, and still is, a debated question, but I believe that at any rate they help to allay the pain.

✓ *Smoking.*—Many patients are inveterate smokers, especially of cigarettes, which means they smoke a little all day long. It is arguable whether they get ulcer symptoms because they smoke so much, or whether they smoke so much because they have the ulcer patient's unstable constitution, but undoubtedly it is the wisest course to forbid tobacco and to advise a small extra meal rather than a cigarette.

When the patients have completed the month's rational cure they may be discharged, but with a number of instructions, preferably written:—(1) Keep to a plain diet for another four months. (2) Take frequent meals, preferably every two or three hours. (3) Take the powder for another three or four weeks, but in decreasing amounts. (4) Abstain from smoking tobacco or smoke only a little.

The most important of these rules is the taking of frequent meals.

Nearly all patients become symptom-free with this cure, but not if there is pyloric stenosis, or if deep, penetrating ulcers exist. It cannot be denied, however, that relapses are common. Months or even years afterwards, the symptoms will return in a considerable proportion of cases. This tendency to relapse seems to be especially marked in duodenal ulcer, the type of peptic ulcer which is becoming more and more common. But the relapse frequency appears to be the same no matter how the cure is modified, and at any rate it is not greater with the freer than with the stricter regime.

TREATMENT OF THE BLEEDING ULCER

It can be said without hesitation that in earlier days the treatment of bleeding gastric ulcer has been dominated by apprehension: fear of permitting move-

ment in bed, of giving anything to drink, of giving anything to eat, and fear of giving blood transfusions. This anxiety has now largely vanished and given place to a boldness in therapeutic methods which has proved advantageous and has dispelled the heavy dramatic atmosphere that previously surrounded these patients. I personally bear a large share of responsibility for this reversal of the principles of the treatment, in that, in 1933, I entirely abandoned the old methods which relied on immobilization and inanition, and introduced the free regime, popularly known as "treatment with food", which consists of prompt and free feeding at short intervals. I have now treated over 1000 patients with profuse hæmorrhage from ulcer by this method and have repeatedly published reports on the results, the last in 1947, with demonstration of the advantages obtained. The method has gradually been adopted throughout the world, sometimes modified by local customs. In England, Witts has accepted the principle, but has somewhat altered the diet.

The treatment I now employ and would recommend for bleeding ulcer, that is to say for hæmatemesis and melæna even in their severest forms, is the following:—

- (1) A full purée diet.
- (2) Ferrous lactate, 2 tablets of 0.25 gm., three times daily.
- (3) One or more blood transfusions in severe cases.

The purée diet comprises the following meals:—

- 6 a.m.—tea, white bread and butter.
- 9 a.m.—oatmeal with milk, white bread and butter.
- 1 p.m.—dinner, including a variety of dishes.
- 3 p.m.—cocoa.
- 6 p.m.—white bread and butter, slices of meat, cheese and tea.

The dinner includes such dishes as the following: meat balls, timbales, broiled chops, omelettes, fish balls, vegetables au gratin, meat au gratin, fish au gratin, mashed potatoes, vegetable purées, vegetable soups, cream of vegetables, stewed apricots, apple sauce, porridge, rice and tapioca puddings, and so on.

The patients are encouraged to eat *ad libitum*; water and milk are put on the table, and they should drink as much as they like.

I chose the purée diet at random. It is in fact merely a mild, non-irritating diet which we had previously used in various simple forms of indigestion. I might just as well have selected another form of diet provided it were free. For it is not a question of a particular diet but of the rule: "Something to eat and drink from the very first day". The way in which it can be varied is determined by the dietetic customs of the particular country and locality.

Large doses of *ferrous salt* are given with a view to promoting blood regeneration, but this is not of great importance because the store of iron in the organism and the free diet are usually sufficient to ensure an optimal blood regeneration. Iron administration possesses a slight disadvantage in that the fæces remain black, so the patient is denied the satisfaction of seeing a return to the ordinary brown colour. But this is a minor incident.

In the great majority of cases a *blood transfusion* will be unnecessary, but in severe cases it will be beneficial or may even save the patient's life. The patients to whom special attention must be paid and in whom it is necessary to be prepared for blood transfusion, are the older ones with profuse or repeated hæmorrhage, particularly when it manifests itself as hæmatemesis. Experience has shown that it is in these cases that the risk is greatest. In young persons and in all cases in which the hæmorrhage only causes melæna the risk is practically *nil*.

The patients are allowed to move freely in bed. After about a fortnight they are permitted to get out of bed in order to go to the W.C., shave themselves, and the like. In about a month's time they are discharged with instructions that they must adhere to a bland diet and take frequent meals as prescribed for painful ulcer. As a rule I give neither alkalis nor belladonna in the treatment of hæmatemesis and melæna, as there is usually no pain.

It is a proven fact that the free diet neither increases hæmorrhage nor provokes repeated bleeding. On the contrary, the mortality from ulcer hæmorrhage—that is, from hæmatemesis and gross melæna—is very considerably reduced with this treatment. In my last report* I had a gross mortality of 2.6 per cent. and a net mortality of 1.5 per cent. Net mortality signifies that the material was free from deaths due to other causes than the hæmorrhage, and from the few patients who did not get as far as treatment. The fatal cases constituted a distinct group: old persons with large chronic penetrating ulcers in whom the hæmorrhages had become evident by hæmatemesis, especially repetitions of it.

The treatment "with food" is pleasant both for patients and nurses. The patients rapidly regain their strength; the blood is soon regenerated, and in a month the anæmia is practically overcome and convalescence at an end.

TREATMENT IN SYMPTOM-FREE PERIODS

I have described how I deal dietetically with ulcer patients in the phases of the disease that urge them to seek advice and treatment, namely, when there is pain or hæmorrhage. But what advice and treatment should be given to patients during the periods when they are free from symptoms and do not seek advice of their own accord? For, as already mentioned, the high relapse frequency with periodic return of the symptoms and the tendency to become chronic show that we have to reckon with a certain *latent* ulcer disease. Unfortunately, too little is known about the factors which give rise to recurrence of symptoms. It is true that nervous factors and mental strain play their part, perhaps also tobacco smoking, cold and infections. But there must undoubtedly be other and unknown factors which help to produce the periodic relapses, often associated with the seasons. I have never been able to see any real evidence that the food is the determining factor, at any rate not the so-called "indiscretions" as regards the diet.

* *Archives of Internal Medicine*, December 1947.

Nevertheless, I am so far guided by tradition that I advise ulcer patients to live "carefully" in the symptomless periods, that is, not to commit too many excesses in eating and drinking. I counsel them—and I think this is important—to eat at regular intervals and *frequently*, to take things quietly, to try to avoid vexations and worries, and to refrain from too much nervous cigarette smoking. I also instruct them to beware of cold and catching chills in spring and autumn. But whether all this is of any use or not I do not know.

INDICATIONS FOR SURGERY

Although the question of which patients should be advised to have an operation is beyond the scope of this article, I should like to give some indications on the basis of which at the present time I advise operative treatment. The risk of operation has on the whole been reduced during the last few years, and especially so in those hospitals and clinics where an expert gastric surgeon is available. However, such skill still varies considerably from one place to another, and consequently the rules for deciding when a patient should be submitted to operation cannot, and must not, be the same everywhere, but must depend upon local conditions and facilities.

In the case of *the non-bleeding peptic ulcer* I now usually take the line that operation, i.e., partial gastric resection, is indicated if the patient has had ulcer symptoms for more than five years, and has had two courses of medical-dietetic treatment without any lasting effect. There may be individual circumstances which may cause me to relax this rule somewhat, and there may be contraindications which may make me less willing to consider operation, but in general the above rule holds good. The gastric surgeon with whom I collaborate has now an operation mortality for his partial gastric resections in non-bleeding ulcers of about 2 per cent.

In the case of *the bleeding peptic ulcer* I have hitherto taken the line of never recommending these patients for operation. The low mortality rate with the free feeding system, the difficulty in selecting the group of patients suitable for surgery, and the great risk so often attaching to the operation in these cases, were the factors which caused me to adopt this attitude. Conditions, however, are now changing: for one thing it is now easier to define and select the small group of bleeding peptic ulcers in which the risk of death from exsanguination is great and in which consequently the question of operation is acute, and secondly, the risk at operation has been considerably reduced, especially by the generous use of blood transfusions. These circumstances have made me reconsider my viewpoint, and I am now more willing to consider operation for some carefully selected cases of severe hæmatemesis, i.e., when the patient is more than forty years of age, has persistent or repeated bleeding manifesting itself as hæmatemesis, and threatens to die in spite of repeated blood transfusions. In addition, there must be no serious contraindications to operation, the presence of an ulcer should have been proved by X-rays, and an experienced surgeon should be available. The operation recommended is a partial resection of the stomach.

THE SURGICAL TREATMENT OF PEPTIC ULCER

By A. HEDLEY VISICK, F.R.C.S.

Surgeon, York County Hospital.

THE problem of the surgical treatment of peptic ulcer is essentially the problem of the management of the *patient* with peptic ulcer. This may be considered at four stages of treatment:—(1) In the investigation department at hospital. (2) In the surgical department at hospital. (3) In general practice after discharge from hospital. (4) In the follow-up clinic.

MANAGEMENT OF THE PATIENT IN THE INVESTIGATION DEPARTMENT AT HOSPITAL

I feel that the hub of the gastric universe is not the operating theatre, but the out-patients department, where investigation, selection and follow-up are conducted. The drama of the operating theatre has for many years obscured the equally important, although less spectacular, work that is done elsewhere, and the importance of the general practitioner, the social worker, and the nursing staff in the team dealing with peptic ulcer patients has not been adequately recognized.

Under the old system of management, it was largely a matter of chance what happened to a patient when he arrived at hospital. If he was seen by a physician he was given a bottle of medicine: if he was seen by a surgeon he was likely to have an operation. In many cases the general practitioner really decided treatment by the address on his letter of introduction. To-day it does not matter whether the patient is first seen by a physician or a surgeon, provided a consultation is held to decide what is the best treatment in each individual case. In some cases the decision is far too difficult for any one individual to make. The united experience and judgment of the whole team should be utilized—physician, surgeon, radiologist, and general practitioner. The general practitioner alone is familiar with the home circumstances of the patient which are so important in affecting the selection of treatment, and therefore he should be made an active member of the team. The time to hold this consultation is not after two or three unsuccessful courses of medical treatment, but the moment investigations have been completed—before, not after, complications have occurred. Perhaps “consultation” is not the right word, for this suggests that after the interview one or other of the parties will fade out of the picture. It would be better if at this stage, “collaboration” between physician and surgeon started, and this collaboration must continue throughout the further course of treatment, whether in medical or surgical wards and, what is even more important, it must extend into the follow-up clinic. Only then will surgeons have an

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select that 50 per cent. of the patients whom we hope will respond permanently—not just temporarily—to medical treatment. We base our selection on the following points:—(a) The length of history and the *severity* of symptoms judged by their effect on the patient's enjoyment of life and efficiency at work; (b) an assessment of the personality and temperament of the patient; (c) the social and economic position of the patient; and (d) an assessment of the local pathology.

The length of history and the severity of symptoms are of the greatest help in selecting treatment. A long history of many relapses suggests destruction and fibrosis. Early recurrence after medical treatment, after acute perforation, or after previous gastro-enterostomy, suggests that further medical treatment is likely to be unsuccessful. Incapacitating pain which fails to respond to medical treatment demands urgent surgery.

The assessment of the personality and temperament of the patient can only be arrived at after careful questioning and listening, and it is important to include the patient's wife in these observations. The letter which the patient brings from his doctor is of the greatest help if it gives his opinion of the patient's emotional type. Will the symptoms remain cured if the ulcer is removed? The patient's own doctor is often in the best position to answer that question.

The social and economic position of the patient will profoundly affect his ability to follow any regime that may be imposed upon him. Apart from the will to keep rules (which depends upon his moral fibre), his ability to obey instructions depends upon the type of his employment, his home and his wife. Here again the opinion of the patient's own doctor is needed.

The assessment of the local pathology rests with the radiologist. Only he can decide if there is a penetration into the liver or pancreas, whether deformity or stenosis is present, whether the ulcer is gastric or duodenal, and if gastric, whether any signs of malignant degeneration are seen. The limitations of radiology should be borne in mind. The degree of deformity is difficult to assess radiologically, and I have often found far more local destruction and deformity than was expected. Gastroscopy will occasionally reveal evidence of malignancy which is missed radiologically, but the more skilful the radiologist, the less the need for gastroscopic confirmation. The exception to this rule is the determination of the time of complete healing of a gastric ulcer. For this, gastroscopy is more accurate than radiology.

INDICATIONS FOR MEDICAL TREATMENT

Two groups must be accepted for medical treatment in spite of their bad prognosis:—(1) Those patients who by reason of their general condition are considered unsuitable for surgery; (2) those who, by reason of their neurotic overlay, are considered unlikely to respond to removal of the organic lesion. Apart from these, we now only advise medical treatment if we think that the patient belongs to that group which is likely to respond permanently to a medical regime. They will include:—(3) Those with

opportunity of observing the excellent results which follow medical treatment in properly selected cases, and physicians will be able to observe the type of patient who does not respond to surgery, and who must be accepted for medical treatment in spite of the unsatisfactory prognosis.

The main purposes of an investigation department are:—(a) To investigate; (b) to confirm diagnosis; (c) to select appropriate treatment.

Investigation.—The essential investigations are the same whether they are carried out by a physician or a surgeon, and there is no need to submit the patient to innumerable laboratory tests. All that is necessary is (1) a careful history and clinical examination; (2) expert radiological examination; (3) a blood count and renal function tests. Tests meals, although valuable for prognosis after operation, are no help in making a diagnosis. Apart from their interest for research purposes, they are not worth the trouble they give the biochemical department, nor the discomfort they cause the patient.

Diagnosis.—Moynihan taught that the clinical diagnosis of duodenal ulcer was both easy and accurate, but we have not been so fortunate, for we have so often found that the history is atypical. Those who give a typical history of ulcer often have no radiological evidence of such, and we have learned to our cost that when radiological evidence of ulcer is lacking, it is extremely unlikely that an ulcer will be found at operation. Those who give an atypical history not uncommonly have positive radiological evidence of ulcer.

After making the diagnosis the most important problems for the physician and surgeon to study are the assessment of the personality and temperament of the patient, and the assessment of the severity of symptoms. Both will have a vital effect on selection of treatment.

Selection of treatment.—Three alternative courses are possible after the diagnosis is established:—

(1) If it is decided that no ulcer is present, and that the patient belongs to the "potential ulcer group", he will return to his own doctor for further palliative treatment, and it is important to recommend a repeat X-ray during the next attack of pain if one should develop.

(2) If the radiologist confirms the presence of an ulcer, but symptoms are mild, it will be found that most patients will refuse bed treatment, and here again they must be treated by ambulatory treatment along palliative lines.

(3) If the radiologist confirms that an ulcer is present, and symptoms are severe, there is a choice between medical and surgical treatment, but before making a selection it is necessary to know what results can be expected. It is not sufficient to be familiar with statistics published from famous clinics. What every practitioner needs to know is the fate that awaits his individual patient if he is referred to the local hospital. Therefore every hospital should produce figures in order that the physician may judge whether *in his locality* it is justifiable to advise surgical or medical treatment.

In view of the fact that only 50 per cent. of those who have been admitted for medical treatment obtained relief for over three years, we no longer insist on preliminary medical treatment for all patients, but we now try to

adequate, results in young men are excellent, and their capacity for work is unimpaired.

MANAGEMENT OF THE PATIENT IN THE SURGICAL DEPARTMENT AT HOSPITAL

For many years surgical treatment has meant operation and then abandoning the patient to his own devices. To-day the operation is regarded as but one short phase or incident in the course of surgical treatment. There is just the same need for repeated explanation and reassurance, both before the operation and in the months which follow, as should be given to the patient treated "medically".

Choice of operation.—Of the many operations which have been used for the treatment of peptic ulcer only three are in common use in this country to-day:—(1) Vagotomy; (2) gastro-enterostomy; (3) gastrectomy.

Vagotomy is dealt with elsewhere. The early results are excellent, but late results are already causing disappointment and anxiety.

Gastro-enterostomy still survives as an excellent operation for bad-risk patients over fifty-five years of age with pyloric stenosis. Mortality is 1 per cent. and results are satisfactory in 90 per cent. of cases. Its effect on acidity is unpredictable, and therefore it is unjustifiable to perform it on patients under fifty years of age. Owing to the danger of malignant degeneration it is not used for patients with gastric ulcer.

Gastrectomy is used with almost equal success for all types of ulcer and for patients of any age. Its purpose is to produce achlorhydria. When possible the ulcer itself is removed, although this is not essential.

Mortality in the last 340 cases I have operated upon was 2.7 per cent. and results are satisfactory in 95 per cent. of 600 patients operated on between 1936 and 1948.

Not all forms of gastrectomy are equally effective, and there is much confusion over the terms gastrectomy, partial gastrectomy and subtotal gastrectomy, for they have no agreed anatomical meaning. It has been shown that the danger of recurrence after operation depends upon the size of the gastric remnant and its blood supply. It would therefore prevent misunderstanding if the operation were described in terms of the exact size of the part which remains, rather than by an estimate of the proportion of stomach thought to be removed.

Most surgeons mobilize the greater curvature up to the gastro-splenic omentum, which makes it possible to do a "three-quarter gastrectomy". If the greater curvature is mobilized still further by dividing all the vasa brevia except one, it is possible to remove a surprisingly extensive additional area of stomach. The fundus, which previously was anchored against the hilum of the spleen high under the diaphragm, now falls away and presents in the wound. The stomach narrows and becomes more tubular so that it is easy to measure the exact length of stomach which is left, usually 2 in. by 5 in. along the lesser and greater curvatures.

A "three-quarter gastrectomy" has proved satisfactory for the majority of patients, but if the possibility of recurrent ulcer developing is to be excluded with confidence, a more radical operation is essential.

Certain patients show a special tendency to ulcer formation. Patients who have perforated on two or more occasions, those who have had a secondary ulcer after gastro-enterostomy, and young men with rapidly emptying stomachs and high acid, all these need more radical treatment. For them I divide every vas brevis and leave a gastric remnant measuring $1\frac{1}{2}$ in. by 3 in. along the curvatures.

Achlorhydria is a point of great importance in prognosis. The more

a short history (less than five years) and few relapses; (4) those who live in a good social and economic position; and (5) those whose symptoms are mild, provided that there is no radiological evidence of penetrating ulcer, pyloric stenosis or marked duodenal deformity.

These are the main indications for medical treatment—so long as a bed is available within a reasonable time. If there is a two or three months' waiting list various unfortunate things may happen. The ulcer may perforate, or a natural remission will occur; a remission of symptoms which does not necessarily mean that the ulcer has healed. Few patients will submit to prolonged rest in bed if they are only admitted to hospital after their symptoms have disappeared.

INDICATIONS FOR SURGICAL TREATMENT

Provided that neurosis is not too prominent, and the general condition of the patient justifies operation, gastrectomy is indicated for the following conditions:—(1) Evidence of penetrating ulcer—organic stenosis; (2) repeated hæmorrhage; (3) repeated perforation; (4) suspicion of malignancy; (5) failure of medical treatment; and (6) for patients who are unlikely to be cured permanently by medical treatment.

If the best results are to be obtained, the physician and surgeon should join together in an equal co-partnership when dealing with patients who have peptic ulcer. The surgeon who is merely interested in the technical details of operating cannot gain a true picture of the many factors involved in the success or failure of his treatment. He cannot afford to neglect the human side of his work. He should carry an equal share of the responsibility for investigation and diagnosis, and he should have an equal opportunity to state his opinion as to what is best for every patient, whether medical or surgical treatment seems indicated.

In the past all interest was concentrated on the process of "healing the ulcer". The far more important problems of keeping the patient well, of observing conditions which lead to relapse, and of providing means to help the patient to avoid those conditions—all these vitally essential services received scanty attention. To-day the scheme of management must be far more ambitious. Not only must the patient be treated as well as his ulcer, but an active interest must be taken in his home, his work and his affections. It is impossible to avoid becoming involved in housing schemes, marriage guidance clinics, unemployment exchanges, and rehabilitation camps. Even the neighbour, or the lodger, may be the primary cause of converting a satisfactory result into a failure. The doctor who thinks only in terms of "ulcer" or "gastritis" will miss what should be obvious—that environment and emotion are just as important as the acidity of the gastric juices.

There is an impression that gastrectomy should not be advised for young men who have a special tendency to ulcer formation. Our results do not confirm this. Of 52 patients under thirty years of age, only two are failures and none has died. Provided special care is taken to make the resection

away in charge of a physician who is not familiar with the post-gastrectomy regime do not do so well as patients who live near enough to be influenced by frequent visits to the follow-up clinic. The position of the general practitioner is made difficult by the conflicting advice that different physicians and surgeons give to their patients on leaving hospital:—Dr. A. likes his patients placed on a strict regime of diet restrictions and limitation of smoking and drinking; Dr. B. believes in the good life and sees no use in restrictions; Dr. C. has no further interest in his patients after discharge provided they are kept out of the way of the surgeon. Loyal team work requires that the treatment for each patient should be continued according to the ideas of the particular physician or surgeon under whose care he was placed while in hospital. This presents an impossibly complicated problem for the practitioner, and causes confusion in the mind of the patient, both of which react unfortunately on his chances of cure.

Not uncommonly, patients who were able to tolerate full diet while in hospital will complain of pain and vomiting a few days after they return home to meet the difficulties and anxieties of home life. Fussy wives and domestic worries may undo in a few days much of the good that has been done while in hospital. For these patients dismissal with a bottle of medicine is worse than useless. What they need is reassurance and a reasonable explanation of their symptoms. The cause of their set-back is most likely to be found in their social environment and their sense of insecurity on leaving hospital. An understanding doctor will soon help them to regain confidence, and with confidence their symptoms will often disappear.

Sixty-five per cent. of patients are completely symptom-free from the moment they become convalescent. They are able to eat anything they like and they remain satisfactory, although some may need reassurance and encouragement occasionally. They are able to return to work within six to twelve weeks, and beyond the regular six-monthly check-up in the follow-up clinic they require no further advice.

Thirty per cent. complain of mild symptoms during the early months after operation. Fullness after meals, bile vomiting, tiredness, sweating or palpitation are the usual symptoms. Roughly half of this group can control their symptoms by resting for ten to twenty minutes after the meal, by limiting the size of the meal, and by avoiding certain articles of diet which they feel disagree with them. Nothing except self-induced vomiting seems to affect the nausea and vomiting of bile, which is the most distressing and the most resistant to treatment. Fortunately all the symptoms gradually diminish in severity and frequency with time, and by the third year only 5 per cent. continue to suffer severely. If simple remedies do not relieve the symptoms the ultimate prognosis will depend upon the temperament and personality of the patient. If he allows his life to be spoilt, the result will be a failure; if he can be encouraged to accept his condition cheerfully he will find the symptoms are seldom severe enough to interfere with his work or recreation.

The small proportion of patients (5 per cent.) who consider their result is a failure are the most difficult to handle. Although some enjoy their misery, it would not be right to suggest that all are neurotic. They will benefit from constant reassurance, re-examination and even occasional therapeutic X-ray screening in the follow-up clinic, so that they can be assured that no recurrence has developed. To the general practitioner and to the specialist they provide a constantly recurring demonstration of the type of patient for whom surgical treatment is unsuitable.

The prescribing of medicine and powders should be avoided, for it is

extensive the resection, and the more complete the devascularization of the remnant that is left, the less likely is a recurrent ulcer to follow gastrectomy. In this series a recurrent ulcer after two-thirds to three-quarters resection followed within eighteen months in five cases out of one hundred and fifty (4.2 per cent.) In the next five hundred gastrectomies, a more radical removal has so far given complete protection against recurrent ulcer, and in 98 per cent of these cases permanent relative achlorhydria has been produced.

Preoperative management.—The majority of patients are admitted straight from their homes to the surgical wards. All preliminary investigations (X-ray, blood count, kidney function tests) are done in out-patients, for the shorter time the patient is kept waiting in hospital, the better for his morale. Forty-eight hours is usually sufficient.

Those patients who are anæmic are suitably treated until their hæmoglobin is as near normal as possible. If the X-ray shows marked delayed emptying time, a long period of evening stomach washouts may be required before œdema subsides and the stomach regains tone. In the absence of delayed emptying, stomach lavage is not given. Prolonged preoperative treatment is, of course, needed in cases of dehydration, vitamin deficiency, or gross malnutrition.

An important part of preoperative management is to encourage new patients to mix with those who have already had their operation. This contact will dispel much of the dread which most patients associate with operation. Arrangements should be made for the almoner to interview every patient, not for purposes of financial assessment, but to provide a more sympathetic and human contact with the hospital. Most patients have anxiety about conditions at home, work, or finance. It is these aspects which the almoner is specially trained to deal with, and use should be made of her experience to the fullest possible extent.

Postoperative management.—When possible all patients are allowed to walk round their beds the day after operation and they are given light diet as soon as they ask for it, usually the third or fourth day. Before they leave the protection of the hospital on the twelfth day, they are given fried fish, sausages and pork pie, in order to impress on their minds that further restriction of diet is unnecessary, and we make sure that the wife has understood this fact. They are also given a card of instructions which emphasizes their essentially normal and healthy prospects. On no account should this card be called a "diet sheet", for to give a man a diet sheet is to make him an invalid for life. Smoking and drinking in moderation are encouraged. By the third evening they will be found seated among the others round the fireside, a surprise to themselves and an encouragement to their colleagues who are due for operation the next day.

MANAGEMENT OF THE PATIENT IN GENERAL PRACTICE

The final result will often depend upon the way in which a patient is handled immediately he returns home, and I have noted that patients who live far

VAGOTOMY IN THE TREATMENT OF PEPTIC ULCER

By WALTMAN WALTERS, M.D., F.A.C.S.

Chief of the Division of Surgery, Mayo Clinic, Rochester, Minnesota.

THE results of follow-up studies are available in 177 cases of peptic ulcer in which vagotomy was performed alone or in combination with other operations on the stomach or duodenum at the Mayo Clinic. In 77 of these cases I performed the operations, and in the other 100, my surgical colleagues at the clinic who are interested in the surgical treatment of gastro-intestinal lesions performed them.

INDICATIONS

Vagotomy seems definitely indicated in cases of recurring ulceration after partial gastrectomy. It has also given excellent results in the treatment of gastro-jejunal ulcers which have followed gastro-enterostomy. These results compare favourably during a two-year period of observation with the results five and ten years after partial gastrectomy for this type of ulcer. The results of vagotomy in duodenal ulcer when the operation is combined with gastro-enterostomy seem little better than when gastro-enterostomy is performed alone. The same may apply in cases in which pyloroplasty with removal of the duodenal ulcer is accompanied by vagotomy.

In a series of cases of gastro-jejunal ulcer recently reported by Priestley and Gibson the average interval between operation and the development of the ulcer was about three and a half years. It is therefore obvious that a longer interval must elapse before it can be determined whether or not vagotomy added to gastro-enterostomy is followed by better results and a lower incidence of recurring ulceration than gastro-enterostomy alone.

RESULTS IN DUODENAL ULCER

The most satisfactory way to determine the results of vagotomy in the treatment of duodenal ulcer seems to be to study the group of cases in which vagotomy alone was performed without other operations on the stomach. Additional operations on the stomach would tend to promote gastric emptying, decrease the amount of gastric secretion, and reduce the acidity of the stomach either by the reflux of alkaline duodenal and biliary secretions through the gastro-enteric stoma, or by removal of part of the secreting surface of the stomach as in partial gastrectomy. In 16 cases in my series of 77, vagotomy was done without other surgical procedure in the treatment of duodenal ulcer. All the patients survived operation. In nine patients (56 per

essential that these patients learn to stand on their own feet and regain confidence in themselves. Alkalis are particularly unsuitable, since the operation has produced achlorhydria. The treatment given by the general practitioner should agree in every respect with the treatment in the follow-up clinic. The giving of conflicting advice can be avoided if the general practitioner makes occasional visits to the follow-up clinic, where difficulties can be discussed with the hospital doctors and the health visitors concerned, and a common line of treatment agreed upon.

It would save much anxiety if patients were warned concerning possible symptoms which may develop after operation. This applies especially to loss of weight, which often reaches 1 to 1½ stones (6.5 to 9.5 kg.). By the sixth month all patients are stabilized and it is quite useless to attempt to regain weight by increasing the diet. All that is necessary is to explain that loss of weight does not necessarily mean loss of strength.

Advice concerning work is important. Shift work, night work and transport work are best avoided for eighteen months after operation, and if necessary a letter to the employer will often result in more suitable employment being provided. Patients with peptic ulcer, like patients with rheumatism, respond dramatically to confident handling and enthusiastic encouragement. Many have become so accustomed to strict dieting that they need careful watching to make certain that they no longer limit their diet in the way they have formerly been taught. The more liberal their diet, the less likely are they to develop anæmia and deficiency diseases, but in spite of full diet 20 per cent. of women do develop microcytic anæmia of a type which usually responds to iron therapy.

MANAGEMENT OF THE PATIENT IN THE FOLLOW-UP CLINIC

An organized follow-up clinic is an essential department in any modern hospital. In the York Clinic the personnel consists of a physician, a surgeon, the radiologist and the almoner. All patients are seen by the surgeon at monthly intervals, if necessary, during the first six months, and thereafter they are transferred to the follow-up clinic for six-monthly interviews. The advantages of this method are:—

(1) It gives us an opportunity to treat any symptoms early, before they become chronic, and in so doing we can prevent treatment in hospital from becoming a mere "patching up" process. We can also make certain that the advice given at hospital agrees with the advice given by the general practitioner, and with the assistance of the health visitor we can confirm if home conditions allow this advice to be carried out.

(2) From our records we can produce reliable statistical reports on which we can base an accurate assessment of the value of our treatment: 99 per cent. of our patients have been successfully followed up; only 5 out of 600 patients have been lost sight of.

(3) The regular examination of patients at all stages after gastrectomy and vagotomy provides valuable material for teaching and research.

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cent.) results were excellent and in seven (44 per cent.) unsatisfactory. All patients who had unsatisfactory results after vagotomy alone for duodenal ulcer had ulcer distress and troublesome disturbances of motility for from four to fifteen months after operation. The disturbances of motility consisted of belching of foul-smelling gas, and diarrhœa.

It is interesting to compare these results of vagotomy with those of partial gastrectomy for duodenal ulcer. In 296 cases in which partial gastrectomy was performed at the clinic in 1946 for duodenal ulcer, the hospital mortality rate was only 2 per cent.; in 1947 it was 0.7 per cent. in 275 cases. There were an additional 23 patients with associated gastric and duodenal ulcer in whom partial gastrectomy was performed without mortality; 11 patients with acute perforating duodenal ulcers; 7 who had additional operations, such as cholecystectomy with partial gastrectomy; and 5 patients with active duodenal ulcers and gastro-jejunal ulcers, making a total of 321 partial gastrectomies with 4 deaths, a mortality rate of 1.2 per cent. The long-term results after partial gastrectomy for duodenal ulcer in many large series of cases reported by numerous observers have been excellent in from 80 to 85 per cent. of cases, good in about 10 per cent., and poor with recurring ulcer in only 2 per cent.

RESULTS IN GASTRIC ULCER

In the treatment of chronic gastric ulcer I believe that partial gastrectomy with removal of the ulcer is the best surgical procedure to employ because of the 20 per cent. chance that the lesion may be malignant and because of the excellent results and absence of recurrence of ulceration after this operation. In 98 cases in which partial gastrectomy was performed at the clinic in 1946 for gastric ulcer, the hospital mortality rate was 1 per cent. In 1947 partial gastrectomy was performed in 116 cases for gastric ulcer, with a hospital mortality rate of 0.8 per cent.

In spite of these good results after partial gastrectomy the effects of vagotomy on chronic gastric ulcer were tried in a few suitable cases. In six of the cases in which the ulcer was small the results were excellent. In two other cases large recurring perforating gastric ulcers developed which necessitated subtotal gastrectomy. In both cases insulin tests indicated that all the nerves had been cut. Both lesions were reported to be benign after detailed pathological examination. In a third case symptoms indicate recurrence.

In the series of 177 cases in which vagotomy was done with and without other gastric operations late results were considered excellent in 79 per cent. of the cases. There were five hospital deaths, or a hospital mortality rate of 2.8 per cent. Disturbances of motility occurred in the immediate postoperative period in 19 cases, and in 14 persisted for three and a half to eighteen months. However, in my 77 cases, five patients (6 per cent.) had proved recurring ulcers and, in addition, nine (about 12 per cent.) had recurrence of the symptoms of ulcer, and the presence of recurrence of the

ulcer could not but be considered. Thus 14 (18 per cent.) of these 77 patients had had a persistence or recurrence of their ulcer symptoms. In 11 of these 14 cases insulin tests after operation gave negative results.

In seven cases of gastro-jejunal ulcer after gastro-enterostomy the gastro-enteric anastomosis and the gastro-jejunal ulcer were removed, continuity of the gastro-intestinal tract was restored, and vagotomy was performed. Two of these patients later had abdominal pain and loss of appetite and weight; craters of recurring duodenal ulcers were seen on X-ray examination months later. This incidence of recurrence is only slightly lower than it is when the same procedures are employed without vagotomy.

INSULIN TESTS

Hollander insulin tests were made in 62 of my 77 cases. They gave negative results in 74.1 per cent. of these cases. Relief of pain of ulcer, reduction of gastric acidity, dilatation of the stomach, and persistent postoperative disturbances of motility were about the same in cases in which results of the insulin test were negative as in those in which they were positive. However, the patients who had proved or suspected recurrence of ulcer were practically all in the insulin-negative group. It would therefore seem that the Hollander insulin test does not always indicate the completeness of vagotomy, or that complete vagotomy is not necessary in every case to accomplish relief of pain and other desirable results.

I am indebted to my First Assistants, Dr. H. A. Neibling, Dr. B. C. Brownson and Dr. S. K. Phillips for supervising the insulin tests and carrying out the review of the results.

RADIOLOGY IN THE DIAGNOSIS OF PEPTIC ULCER

By G. R. MATHER CORDINER, M.B. D.M.R.E.

Radiologist, St. George's Hospital.

RADIOLOGICAL examination is the most practicable and most reliable method for diagnosing peptic ulcer. Even with a typical history the clinician can never be quite certain that an ulcer is present. A similar history may be obtained in cases of other organic diseases of the alimentary tract and may be present in cases of functional disorders. Moreover, an ulcer may exist with an atypical history. In competent hands, the accuracy of the radiological investigation exceeds that of the clinical examination or of any other laboratory method. By means of the X-ray, the clinician can obtain an anatomical demonstration of the ulcer and its site can be fixed. The presence of complications, unsuspected from the clinical examination, will often be revealed. The perforation of an ulcer into an adjacent organ may be shown. The existence of an hour-glass contraction or a purse-bag contraction of the stomach and the presence of gastric retention can be demonstrated. An ulcer, clinically benign, will often be shown to be malignant. Finally, radiology is the most practical routine method to check the response of an ulcer to treatment and to determine when an ulcer has healed. Thus, in addition to establishing the diagnosis on an objective basis, the radiological findings will often influence the clinician in his choice of treatment for a particular case. This does not, however, mean that the X-ray examination can be substituted for a careful clinical examination or dispense with the need for other laboratory investigations. A careful clinical examination is still essential and other laboratory investigations must be carried out when necessary.

THE X-RAY EXAMINATION

The examination consists of (1) the study of the mucosal pattern of the stomach and duodenum, and (2) the examination of these organs after they have been filled with an opaque meal.

The patient is given a mouthful of an opaque meal. After following the course of this mouthful through the œsophagus into the stomach, the examiner distributes it over the mucosal surface of the stomach by manual manipulation. The uniform distribution of the meal is facilitated by varying the position of the patient. It is not always possible at this stage of the examination to express sufficient meal through the pylorus to demonstrate the mucosal pattern of the duodenum, and its study has to be postponed until a later stage of the investigation.

The examination and demonstration of the mucosal pattern are important for two reasons:—(1) With the demonstration of a normal mucosal pattern

in the stomach and duodenum, the examiner can exclude organic disease of these organs which will give rise to symptoms, and (2) at this stage of the examination ulcers and other organic lesions can be shown which are completely hidden when the stomach and duodenum are filled with the opaque meal.

The patient is then given the remainder of the opaque meal to drink and the silhouettes of the filled stomach and duodenum are examined, through all degrees of obliquity and with varying positions of the patient. The employment of a tilting couch is essential so that the patient can be examined in any position between the erect and the Trendelenburg. Local pressure is applied to show particular areas to the best advantage and this applies especially to the first part of the duodenum, or duodenal cap, where more than 95 per cent. of duodenal ulcers are found. By carefully applying this local pressure, the examiner can displace the surplus opaque meal from any area and bring into relief the mucosal pattern.

With modern equipment, it is possible to obtain what, to all intents and purposes, are instantaneous exposures of films at any moment during the course of the examination. These films may give a general view of the stomach and duodenum or may be localized views of special areas, with or without the application of controlled pressure. All exposures are made under screen control. These permanent records enable the radiologist to demonstrate an ulcer or other organic change in the stomach or duodenum, so that there can be no doubt as to its presence. No longer need the radiologist rely mainly or exclusively for his diagnosis upon the visual impressions of the screen examination. With adequate apparatus and strict attention to radiographic technique, every ulcer or organic change seen at the screen examination can be shown on the films. In addition, lesions which the examiner missed at the screen examination will often be shown on these films. Contrary to the generally expressed radiological opinion, the converse is not the case—that ulcers and other organic changes can often be seen at the screen examination when they cannot be shown on films. It is entirely a question of adequate apparatus and technique and the exposure of an adequate number of films.

Contraindications to the examination.—The contraindications to the X-ray examination in cases of suspected ulcer are few. No patient should be sent for an X-ray examination of the stomach and duodenum whose general condition will not allow of an adequate investigation being made. It is inadvisable to make a routine X-ray examination too soon after an acute hæmorrhage. It is a common experience that, in a large percentage of cases, it is not possible to demonstrate an ulcer when the X-ray examination is carried out immediately after a recent acute hæmorrhage. In these cases, the ulcer crater may be filled with blood clot so that the opaque meal cannot enter it or, as the result of the local blood-letting, the difference in level between the ulcer crater and the surrounding mucous membrane is so slight that the ulcer cannot be shown. It is also held that the manipulation inseparable from the X-ray examination may cause a recurrence of the

bleeding. For these reasons it is best to wait two to three weeks after an acute hæmorrhage before carrying out an X-ray investigation.

THE MUCOSAL PATTERN OF THE STOMACH AND DUODENUM

Figures 1 and 2 are examples of typical mucosal patterns in the normal stomach and duodenum respectively. Just as no absolute standard can be laid down for the normal stomach as seen radiographically, so also is this the case for the patterns formed by the mucosal folds. The patterns formed are many, yet, in spite of these variations, a basic pattern can be identified.

In the *cardiac portion of the stomach*, a fine network of folds is often present. From the cardia, the mucosal folds run longitudinally through the body of the stomach, parallel with its axis. At the *incisura angularis* (the angle formed by the junction of the body with the pyloric portion of the stomach at the lesser curvature) the folds continue directly to the pyloric canal, or they tend to diverge and become curved or spiral towards the greater curvature. In the body of the stomach the folds become more complex as the greater curvature is approached. Here, many of the folds, as they bend to reach the opposite wall, are seen in an axial projection, giving the greater curvature a serrated appearance.

In the *duodenal cap*, the mucosal folds show a similar parallel, longitudinal arrangement.

The mucosal folds in the stomach and duodenal cap are not constant anatomical structures nor are they due to a passive process resulting from the contractions of the muscular coat. The folds have an independent mechanism and they vary in appearance from time to time, these alterations being conditioned by contractions of the *muscularis mucosæ*.

X-RAY SIGNS OF ULCER

The only absolute radiological criteria for the diagnosis of an ulcer are:—(1) The niche; (2) the filling defect; and (3) the accessory pocket.

The niche.—Although historically the term “niche” refers to the X-ray appearance of an ulcer projecting from the profile of the stomach, it is now used more universally to denote the barium-filled projection from the stomach or duodenum as it is seen in any plane. The niche is the most common X-ray sign of an ulcer and is found in more than 90 per cent. of cases. Two forms of the niche are generally described: (1) the *en face* niche, the radiological manifestation of the ulcer as it is seen in a frontal view or end-on from the mucosal surface of the stomach or duodenum, and (2) the *profile* niche, the barium-filled projection from the profile of the stomach or duodenum. Whenever possible, it is the aim to demonstrate the ulcer in these two views, usually at right angles to each other. An ulcer on the lesser curvature of the stomach can only be shown in profile. Technical difficulties in radiography make its demonstration *en face* impracticable.

The *en face* niche is seen as a central barium deposit corresponding to the ulcer crater, surrounded by a translucent halo or ring wall (fig. 3) or with a convergence of mucosal folds towards it (fig. 4). The halo is due to the swollen mucous membrane surrounding the ulcer, projecting into the lumen of the stomach or duodenum and displacing the barium from the immediate vicinity of the ulcer. The convergence of the mucosal folds to the crater is produced by the independent movement mechanism of the mucous membrane in the case of a recent ulcer or by a cicatricial indrawing of mucosal folds to the crater in the case of a chronic ulcer. The *en face* niche is, as a rule, only seen during the examination of the mucosal pattern, being hidden when the stomach and duodenum are completely filled with the opaque meal. It can then be brought into view by applying localized pressure to get rid of the overlying barium.

The profile niche shows as a projection from the outline of the stomach or duodenum. On either side of this projection there is a concave indentation of the adjacent outline of these organs (fig. 8). This biconcave indentation is due to the swollen mucous membrane surrounding the crater, or to the heaping-up of mucosal folds around the ulcer. It is the counterpart of the halo or converging mucosal folds of the *en face* view. This biconcave indentation of the adjacent outline is an essential feature of a profile niche and its presence enables a differentiation to be made from non-ulcer projections from the outline of the stomach or duodenum—for example, a diverticulum or a peristaltic bulge.

The filling defect.—A proportion of ulcers do not show themselves radiographically as a niche but as a filling-defect of the profile of the stomach or duodenum (fig. 5). These are benign recent ulcers with minimal inflammatory changes in their neighbourhood: (1) on the greater curvature and on the anterior or posterior walls of the stomach near the greater curvature, and (2) on the anterior or posterior walls of the duodenal cap. The filling-defect is circular and has a double outline. In the above mentioned situations, the mucous membrane is loosely attached to the deeper layers of the gastric and duodenal wall. By virtue of the independent movement mechanism, the mucosal folds can overlap each other so completely from all sides that they can seal off the ulcer from the lumen of the stomach or duodenum. The barium cannot enter into the crater and so a niche cannot be demonstrated. The overlapping of the folds over the ulcer from all sides produces the double-outlined circular defect of the profile.

A filling-defect is not found with a benign recent ulcer on the lesser curvature of the stomach. Here, the mucous membrane is firmly attached to the deeper layers and its independent movement mechanism is correspondingly limited. On account of the firm attachment of the mucous membrane to the deeper layers the mucous membrane folds cannot alter their number, height or direction sufficiently to overlap the ulcer completely and switch it out of the lumen of the stomach. A recent ulcer of the lesser

curvature with minimal inflammatory changes in its neighbourhood will therefore always give rise to a niche. A filling-defect may, however, be found with a chronic ulcer on the lesser curvature of the stomach. A chronic ulcer which has involved the deeper layers of the wall of the stomach and in which fibrosis and scar-tissue contraction have taken place, usually has high edges which overhang the crater. In some instances the mucous membrane may actually become enfolded over the ulcer. If, with such an ulcer, there is much swelling of the adjacent mucous membrane as the result of gastritis, the entrance to the crater may be completely blocked by the swollen mucous membrane and the barium is unable to enter the crater. No niche is therefore visible, but instead, there is a filling-defect of the profile. As in the case of a recent ulcer on or near the greater curvature, the filling-defect has a double outline.

The filling-defect due to a benign ulcer has to be distinguished from the filling-defect produced by a carcinoma. The filling-defect due to a new growth is usually sickle-shaped. It has a single outline and where the growth and healthy mucosa meet, the mucosal folds break off sharply, as if they had been cut by a knife (fig. 9).

The accessory pocket.—When an ulcer has slowly perforated through all the coats of the stomach or duodenum and has become adherent to, or excavated into, adjacent tissues and is walled off by adhesions, an accessory pocket is formed. The organs most commonly involved are the liver or pancreas, but occasionally the abdominal wall or spleen is involved. In the erect position, an accessory pocket, instead of showing as a homogeneous shadow when filled with barium, often shows the presence of three layers: (1) a dense layer of barium at the lower pole of the pocket, surmounted by (2) an intermediate fluid layer, and capped by (3) an air bubble. Barium is likely to remain in the pocket when the opaque meal has left the stomach and duodenum. An accessory pocket in the liver is likely to move with respiration; one in the pancreas remains stationary. With rare exceptions, an ulcer giving rise to an accessory pocket is benign.

THE HOUR-GLASS STOMACH

Radiology is the only means by which a diagnosis of hour-glass contraction of the stomach can be made. The organic form is the result of contraction in the transverse diameter of the stomach. The radiological diagnosis is easy. The stomach is biloculated, the two loculi being connected by a narrow channel of varying length. This narrow channel is situated in the long axis of the stomach, near the lesser curvature. An active ulcer may be present and is usually found at the upper limit of the narrow channel (fig. 6). The hour-glass contraction is never quite so narrow in the actual specimen as shown radiographically, being accentuated by superadded spasm and swelling of the mucous membrane in its neighbourhood. Usually, the hour-glass stomach shows delay in the emptying of its contents.



FIG. 1.—Normal gastric mucosal relief.

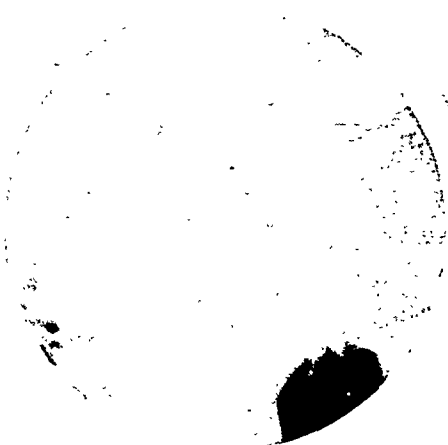


FIG. 2.—Normal duodenal cap mucosal relief.



FIG. 3.—Duodenal ulcer, with halo—*en face* view.



FIG. 4.—Gastric ulcer, with converging mucosal folds—*en face* view.

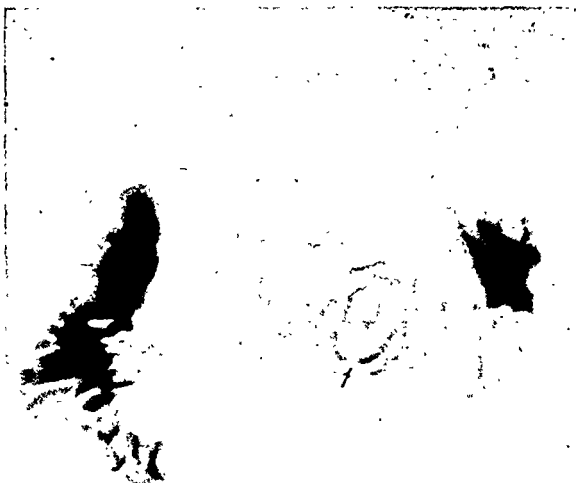


FIG. 5.—Benign gastric ulcer—double-contoured filling defect sign.

FIG. 6.—Hour-glass stomach, with ulcer.



FIG. 7.—Purse-bag stomach.

FIG. 8.—Gastric ulcer, showing biconcave indentation of adjacent profile.



FIG. 9.—Gastric carcinoma—single contoured filling defect.

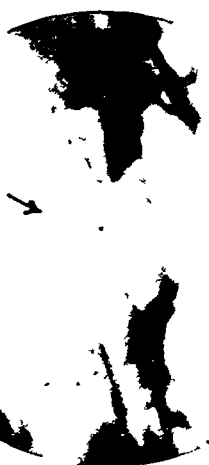


FIG. 10.—Malignant gastric ulcer.



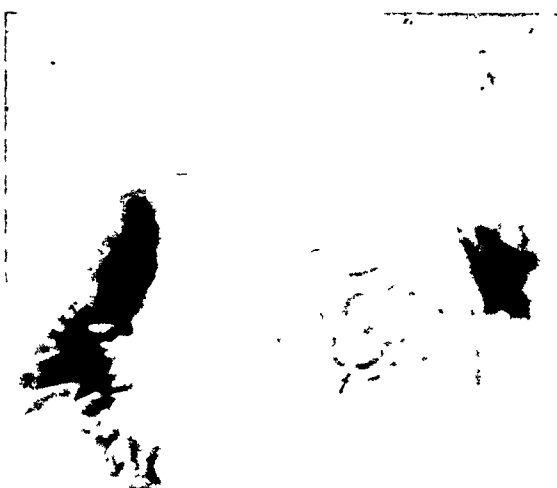


FIG. 5.—Benign gastric ulcer—
double-contoured filling defect
sign.

FIG. 6.—Hour-glass stomach,
with ulcer.



FIG. 7.—Purse-bag stomach.

THE PURSE-BAG STOMACH

The purse-bag stomach or snail-rolling of the lesser curvature is a relatively uncommon complication of gastric ulcer. Its diagnosis can only be made radiographically, for it does not give rise to any typical clinical picture. The condition results from a shortening of the lesser curvature, due to scar tissue contraction in or about the wall of the stomach. The contraction takes place mainly in the long axis of the stomach, as opposed to the transverse contraction which gives rise to the organic hour-glass stomach. The condition is characterized by an extreme degree of flexion of the pyloric portion upon the body of the stomach (fig. 7). The pylorus is drawn upwards towards the cardia, so that an ulcer of the body of the stomach may appear to be pre-pyloric in situation. It is impossible to separate the pyloric portion from the body of the stomach, either by manipulation or by change of position. In a pronounced case, the greater part of the purse-bag is formed by the greater curvature of the stomach. As a rule, the gastric emptying time is prolonged up to twenty-four or forty-eight hours, due to constriction of the pyloric opening by perigastric adhesions. In this condition it is often impossible to demonstrate an active ulcer. Even the surgeon at operation may be unable to find the primary cause on account of the extensive perigastric adhesions which are present. Sometimes an hour-glass contraction and a snail-rolling of the lesser curvature are present in the same case.

THE MALIGNANT ULCER

Radiology can only show the macroscopic character of a lesion and more must not be expected of it than can be learned from inspection and palpation of the resected specimen. An ulcer which is clinically benign, and which on inspection and palpation appears to be benign and is only proved to be malignant on microscopic examination, will as a rule show the radiographic characteristics of a benign ulcer.

An ulcer niche, more than 2.5 cm. in diameter, is usually, but not invariably, regarded as malignant. This is by no means a reliable sign. A more suspicious sign that an ulcer may be malignant is the presence of a rigid niche with an absence of cicatricial changes in its immediate neighbourhood. Careful search of the mucous membrane in the immediate vicinity of the ulcer will often yield evidence which will raise suspicion almost to a certainty. The earliest sign of malignancy is a small, stiffened mucosal fold of cartilaginous consistency usually to be seen at one margin of the niche (fig. 10). This fold goes "against the grain" of the folds in the affected region and has no relation to the normal fold formations. At the lesser curvature this fold is invariably transverse in its direction, and transverse fold formation is never found at the lesser curvature of the stomach except in cases of malignancy. In the remainder of the mucosa surrounding the ulcer the fold formation is usually obliterated. A study of the mucosal fold



FIG. 11.—Deformed duodenal caps, due to healed ulceration.
No niche present to indicate active ulcer.

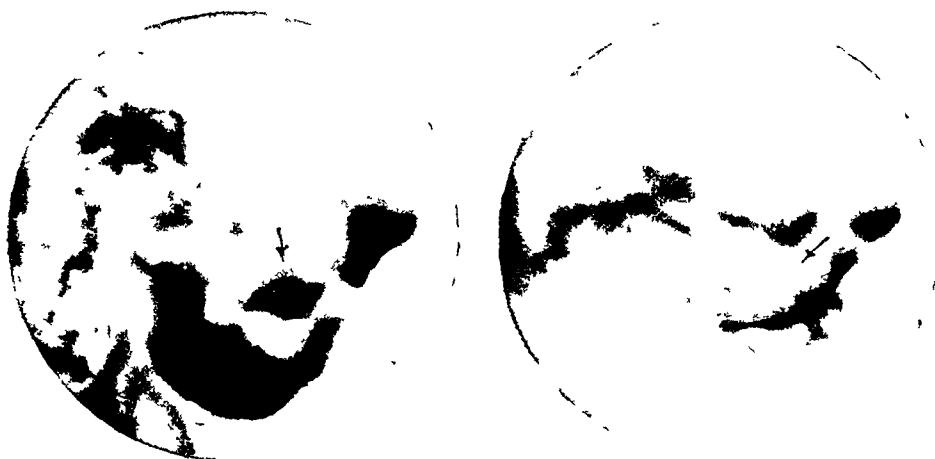


FIG. 12.—Duodenal ulcer. (a) *En face* niche.
(b) After treatment, showing ulcer scar.

dividually by these components of the narrowing in causing obstruction. The narrowing may cause difficulty, but not necessarily delay in the emptying of the stomach. At first, the stomach overcomes the narrowing by a hypertrophy of its musculature and an increased motor activity, so that the stomach empties more rapidly than normal or within normal time. As in cardiovascular disease, one may speak of a "compensated stenosis". In these cases, the cause can usually be demonstrated radiographically. As the narrowing becomes more pronounced, weakening of the gastric musculature with diminished peristaltic activity gradually results in delay in the emptying of the stomach. To the hypertrophy is added a dilatation, affecting first the pyloric antrum but later affecting the entire stomach. One may then speak of a "decompensated pyloric stenosis". In these cases, the delay in the emptying of the stomach may be great, even up to several days.

In the decompensated case, the differential diagnosis often presents difficulty. In many cases, the statement that a gastric retention exists must suffice, leaving the cause unexplained, for it may not be possible to force the opaque medium through the narrowing, either by palpation or by positioning of the patient.

THE HEALING OF AN ULCER

Radiology is the most practical routine method for showing the response of an ulcer to treatment and for determining when an ulcer has healed. The radiological evidence of healing consists in (1) the demonstration of an ulcer scar, (2) the demonstration of a normal mucosal pattern at the site of a former ulcer, and (3) the disappearance of the niche. Obviously, the demonstration of the ulcer scar is the most valuable evidence, for it is the anatomical evidence that the ulcer has healed (fig. 12). Unfortunately, many cases of both gastric and duodenal ulcers may heal without leaving any visible scar formation on the mucosal surface. In these cases, reliance must be placed upon the demonstration of a normal mucosal pattern and the disappearance of the niche. This has been proved to coincide with complete healing of the ulcer in the majority of cases. In making his final observations the radiologist cannot depend upon the screen examination, as the shadows are often too faint to see. The patient must be turned into the identical position used at the previous examination to show the ulcer. Compression must be applied to clear the field and an adequate number of films must be exposed.

formation in the region of an ulcer at or near the greater curvature will usually enable a differentiation to be made between a benign and a malignant ulcer. During the process of healing, a benign ulcer in these situations draws folds towards it from the opposite wall of the stomach. Thus, an ulcer on the posterior wall near the greater curvature draws a fold from the anterior wall and *vice versa*. If the ulcer is malignant, this fold formation is absent.

Finally, the response of an ulcer to treatment may give an indication whether it is benign or malignant. An ulcer which does not diminish in size during treatment, or even increases in size, must always be regarded with suspicion, and its progress must be carefully controlled by repeated examinations and by careful search in its vicinity for early mucosal signs of malignancy. An ulcer which refuses to heal, despite adequate and prolonged medical treatment, must be regarded with great suspicion.

THE DEFORMED DUODENAL CAP

Deformity of the duodenal cap has been, and still is, regarded as a basic sign of an active duodenal ulcer. Every ulcer which has involved the deeper layers of the duodenal wall will leave a residual deformity of the outline of the duodenal cap after the ulcer has healed. In the absence of a niche, there are no criteria by which the radiologist can distinguish a deformity produced by an active ulcer from a deformity produced by healed ulceration. Scar-tissue contraction, inflammatory changes and spasm, either singly or in combination, may all play a part in the production of a deformity of the cap. Since the niche can be shown in 90 per cent. of cases, the diagnosis of an active duodenal ulcer based solely on a deformed cap is seldom, if ever, justified. Some of the most deformed caps are to be seen in patients with no demonstrable ulcer, with no symptoms and with no change in the emptying time of the stomach (fig. 11). These deformities are the result of scarring changes following healed chronic ulceration and by no means necessarily indicate the presence of an active ulcer. Taken in conjunction with the clinical examination and with the results of other laboratory investigations, a subjective diagnosis may be justified when a deformed duodenal cap is the sole radiological evidence. Such a diagnosis, however, should be made by the clinician and not by the radiologist.

PYLORIC STENOSIS

Under this term is included a number of lesions causing obstruction to the passage of food from the stomach and producing a gastric retention of varying degree. The most common cause of gastric retention is a narrowing of the duodenal lumen, either due to a blocking of the lumen by an ulcer or to scarring changes causing a stricture of the duodenum. Spasm and inflammatory swelling may be added to the organic lesion. It may be very difficult at the radiological examination to estimate the part played in-

Similar changes have been noted by Avery Jones (1947) in cases of hæmatemesis. Before 1920, nearly 50 per cent. of all British cases occurred in women under forty, a group which is now responsible for no more than 5 per cent. of hæmatemeses.

Illingworth, Scott and Jamieson's (1944) figures provide a good illustration of the recent trend in perforations. They analysed the admissions to all the Glasgow hospitals between 1924 and 1943 and were able to conclude that the incidence per 100,000 population doubled between 1924 and 1934, and that this increase was entirely attributable to juxta-pyloric (including duodenal) ulcers in men. Altogether, the sex ratio in their series was 19 males to one female.

Similar conclusions were reached by Bager (1929) from a study of 1,495 cases treated in 50 hospitals in Sweden. Over a 15-year period, the total number of treated perforations increased threefold, an increase which was similarly attributable to an increase of juxta-pyloric ulcers in men. It can, of course, be argued that the general increase was due to improved diagnosis and transport facilities, but there would appear to be no reason why such factors should result in a selective increase in the number of perforations in one area of the susceptible gut. It is surely more reasonable to deduce that there has been a real increase. This conclusion is supported by the Registrar-General's figures for the mortality of peptic ulcer in this country. Tidy (1944) has collected the figures between 1912 and 1937 and, although it is not possible to make an accurate assessment of the site of the ulcers in the Registrar-General's figures (for instance, deaths reported as being due to peptic ulcer are classified with gastric ulcers), it is significant that whereas there has been a 50 per cent. increase in the total population over the age of twenty during this period, the increase is confined to men and is greater for duodenal ulcers. The outstanding feature, in the other reports, is the sharp decrease in the deaths due to perforated gastric ulcers in young women (table 1).

TABLE I
CRUDE DEATH RATES PER MILLION LIVING

	MALES		FEMALES	
	20-39 years	Over 40 years	20-39 years	Over 40 years
<i>Gastric ulcer</i>				
England				
1912	43	127	63	94
1921	44	136	28	82
1931	49	260	13	96
1937	46	273	8	89
Scotland				
1912	51	178	70	137
1921	55	215	31	123
1931	46	195	18	117
1937	43	259	1	119
<i>Duodenal ulcer</i>				
England				
1912	27	70	4	16
1921	26	74	4	13
1931	27	147	4	19
1937	28	150	2	24
Scotland				
1921	30	88	7	23
1931	70	259	5	30
1937	79	300	4	36

GEOGRAPHICAL DISTRIBUTION

Another vital clue may rest in the curious geographical variations in the incidence of peptic ulcer. It is said that peptic ulcer is almost unknown in primitive communities but there are, unfortunately, few morbidity studies

ENVIRONMENTAL FACTORS IN THE ETIOLOGY OF PEPTIC ULCER

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GASTRIC and duodenal ulcer is an important disease of modern life and its impact is felt particularly in hospital medicine. It accounts for approximately 10 per cent. of all adult admissions to general medical or surgical wards and for an appreciable proportion of all new cases attending the consulting out-patient clinics. Approximately 15 per cent. of out-patients have dyspepsia for investigation, and of these, well over a half can be shown to have organic disease of the stomach or duodenum, mainly peptic ulceration.

Four reasons suggest that environmental factors are of importance in the etiology of peptic ulcer. First, there has been a great increase in peptic ulcer during the past thirty years; secondly, there are curious geographical differences in the incidence of ulcer and in the ratio between gastric and duodenal ulcer; thirdly, there are differences in the incidence between the social classes; fourthly, differences have been reported in the risk of developing ulcer in different types of occupation.

INCIDENCE

The changing incidence of peptic ulcer in recent years has been particularly interesting. The literature from several European countries has been reviewed by Jennings (1940). This makes it clear that, even if it is impossible to reach any definite conclusions with regard to the total incidence of perforated ulcers, there have been major changes with respect to the sex and age distributions.

At the beginning of the nineteenth century, when perforations began to be reported at all frequently, they almost all occurred in young women: between 1850 and 1900, out of every six perforations three occurred in women under twenty-five, one in an older woman and only two in men. Moreover, most of the perforations occurred in the region of the cardia. In sharp contrast, nine out of ten perforations since 1920 have occurred in men, whilst the tenth has usually been in a middle-aged woman. No matter whether the statistics of England, Germany, France or Scandinavia are studied, the same trend appears; in all of them, perforations in young women are seen to have practically ceased soon after the beginning of the century. In men the increase of perforations has been almost entirely confined to one group, namely duodenal and juxtapyloric in young and middle-aged men, and these appear to have increased three to six times. Perforations of the proximal part of the stomach in men appear to have resembled ulcers in middle-aged women and these have remained practically constant.

* Full-time worker with the Medical Research Council.

of fatal cases. They classified them into the five customary social groups:—

(1) Leading professions, wealthy independents, directors and managers in certain finance and insurance occupations (2.5 per cent.).

(2) Employers and managers in mining, industry, transport, retail and wholesale trades, lower professions and commercial employees in a few occupations carrying a measure of independence (14 per cent.).

(3) Skilled workers, salesmen, shop assistants and clerical workers (49.2 per cent.).

(4) Semi-skilled workers and agricultural labourers (17.8 per cent.).

(5) Unskilled workers (16.5 per cent.).

The figures in parenthesis indicate the proportion of each group in the adult male population.

TABLE 3

SOCIAL GROUP	AGE GROUP						
	20-25	25-35	35-45	45-55	55-65	65-70	70 plus
(a) Male mortality from gastric ulcer per 100,000 living							
1 and 2	1	3	8	17	24	37	39
3	2	4	12	25	31	32	36
4	2	6	15	27	29	28	29
5	2	8	19	31	31	27	31
(b) Male mortality from duodenal ulcer per 100,000 living							
1 and 2	1	3	6	13	19	24	35
3	1	3	7	13	15	18	18
4	2	4	8	11	13	14	13
5	1	4	9	14	14	13	15

It will be seen that, with duodenal ulcer, there is remarkable uniformity in mortality in the different social strata until the age of sixty-five and over, when the mortality is sharply increased in the upper classes. With gastric ulcer, it will be seen that below the age of sixty-five the mortality increases with descent in the social scale, but the figures are reversed for over sixty-five when, as with duodenal ulcer, the mortality is greater in the upper classes (table 3).

The picture of a disease changing in incidence over the past 50 years and varying in frequency in different countries suggests that environmental factors in the life of the individual are at work. Such environmental factors could be a change in feeding habits, the production of a toxic substance in processing foods, increased smoking or alcohol consumption, an increase in forms of work which might adversely affect the gastro-duodenal tract, a mass psychological change of outlook on life or some entirely unrecognized factor in modern life. If occupational factors are at work, they could possibly operate in several ways. One possibility is that specific toxic hazards might damage the gastric and duodenal mucosa. Exposure to lead was, at one time, thought to provide such a hazard but there is no satisfactory evidence of such an effect. Another possibility is that shift work and irregular hours, with the consequent irregularity of meals, might pre-

to allow a precise comparison of the incidence in civilized communities. In the absence of adequate estimates of total incidence, the existence of geographical differences is clearly shown in the gastric:duodenal ratio reported from different countries (table 2).

TABLE 2

<i>Country</i>	<i>Authority</i>	<i>Period</i>	<i>No. in Series</i>	<i>G.U. : D.U. Ratio (Men)</i>
North Norway	Schanke (1946)	1941-44	232	1 : 0.4
Switzerland ..	Mirault-Kretschmar (1945)	1938-44	1522	1 : 1.3
Belgium ..	Hillemand & Sarrazin (1946)	1943-45	1001	1 : 2.2
Norway ..	Knutsen & Selvaag (1947)	1942	556	1 : 2.2
England ..	Avery Jones & Pollak (1945)	1943-44	952	1 : 3.1
Sweden ..	Ihre & Muller (1943)	1930-40	1193	1 : 4.2
U.S.A. ..	Eusterman (1947)	1941-45	—	1 : 12.1

Even within the British Isles considerable differences have been reported. In Stewart and Winsor's (1942) series the gastric:duodenal ratio in London between 1937 and 1940 was 1:1.6, whilst Houston's (1946) series from Newcastle gave a ratio of 1:8.8 for the years 1939-44. Similarly, Tidy's figures showed a disproportionate rise for the male mortality from duodenal ulcer in Scotland up to 1937, a disproportion which is the more significant in view of the similar trends of the female mortality rates in England and Scotland.

One important factor responsible for geographical differences appears to be the proportion of town dwellers. An analysis of the Registrar-General's peptic ulcer mortality figures by Morris and Titmuss (1944) showed that the mortality rates for peptic ulcer for men over forty-five have been approximately 75 per cent. higher in the County of London than in the rural areas of England and Wales. Bager (1929) found that 60 per cent. of perforations from selected hospitals in Sweden were from rural areas, and official statistics estimated that 72 per cent. of the population were rural. In Italy, Ginanneschi (1938) estimated that the incidence among urban workers was $3\frac{1}{2}$ times that among agricultural workers. The objection to these figures is that it may be easier to arrange hospital admission or investigation of urban than of rural workers; whilst the apparently lower mortality rates may have been due to less efficient diagnosis.

The existence of these geographical differentials adds support to the contention that gastric and duodenal ulcers are two distinct diseases. Further evidence in favour of the viewpoint comes from an analysis of the social factor in peptic ulcer mortality, and this may provide an important clue.

THE SOCIAL FACTOR IN PEPTIC ULCER MORTALITY 1930-32

Morris and Titmuss (1944) analysed the decennial supplement statistics from the Registrar-General's return, which gave details of the occupation

of fatal cases. They classified them into the five customary social groups:—

(1) Leading professions, wealthy independents, directors and managers in certain finance and insurance occupations (2.5 per cent.).

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5	2	8	19	31	31	27	31
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The picture of a disease changing in incidence over the past 50 years and varying in frequency in different countries suggests that environmental factors in the life of the individual are at work. Such environmental factors could be a change in feeding habits, the production of a toxic substance in processing foods, increased smoking or alcohol consumption, an increase in forms of work which might adversely affect the gastro-duodenal tract, a mass psychological change of outlook on life or some entirely unrecognized factor in modern life. If occupational factors are at work, they could possibly operate in several ways. One possibility is that specific toxic hazards might damage the gastric and duodenal mucosa. Exposure to lead was, at one time, thought to provide such a hazard but there is no satisfactory evidence of such an effect. Another possibility is that shift work and irregular hours, with the consequent irregularity of meals, might pre-

dispose to ulcer formation as a result of the exposure of the mucosa to undiluted gastric juice for long periods at a time. This has been held to be the explanation of the assumed high incidence of ulcer among transport workers. Finally, occupation might be connected with psychosomatic factors, the responsibility and anxiety resulting from some forms of work being actively concerned with the development of duodenal ulcers in particular.

Occupational factors.—The literature on occupational differences in the incidence of peptic ulcer is conflicting. The most general view is summarized by Avery (1940) when he says: "The highly strung individual whose work involves a high pitch of nervous tension and worry, with irregular hours of work and irregular meal times is particularly liable to succumb to peptic ulcer. Amongst hospital patients, the incidence is highest among waiters, taxi drivers and transport workers, while in private practice, an unusually high proportion of medical men and women are seen." Hurst and Stewart (1929) found an unduly high proportion of ulcers among physicians, and Crohn (1927) and Ryle (1932) had similar impressions from their experience. In Alsted's (1942) and Ginannesschi's (1938) series the incidence of ulcer was high among professional and intellectual workers, but Ihre and Muller (1943) found that it was low. Schellong (1937) and Jennison (1938) reported a high incidence in building workers. Duesberg (1938) obtained a high incidence in foundry workers and labourers, whilst according to the Scottish Report on Incapacitating Sickness (Department of Health for Scotland, 1935) miners had a worse experience of peptic ulcer than the rest of the male insured population. In contrast, Ihre and Muller (1943) and Castrovilli (1937) found that the incidence in labourers was low. General agreement has only been obtained for two groups of workers, namely transport workers, in whom Ihre and Muller (1943), Sallstrom (1945), Ginannesschi (1938), and Castrovilli (1937) have all found high incidences, and agricultural workers, in whom the incidence has been commonly reported to be low (Ihre and Muller, 1943; Alsted, 1942; and Ginannesschi, 1938). By themselves none of the above reports are convincing as they are all open to major statistical criticisms, for example, sex differences have often, and age differences have nearly always, been neglected. However, in so far as they agree, they must be taken to provide presumptive evidence of occupational differences. By far the most convincing individual report is that of Schanke (1946), who has demonstrated a remarkable excess of gastric ulcers among the fishermen of northern Norway; he attributes this mainly to the extremely irregular meals which the fishermen are subject to in the course of their work.

The whole question of occupational incidence has been the subject of a recent survey which is at present being prepared for publication (Doll and Avery Jones). The preliminary results from a survey of 6000 people in different occupations appear to show a remarkably even incidence among

skilled workers, without any increased risk among bus drivers or conductors. Doctors, managers and foremen carried a higher incidence, and agricultural workers were least affected. The duodenal ulcers were evenly distributed throughout the social classes but there was a preponderance of gastric ulcers among the poorer members of the community. Irregular meals, shift work, and smoking have not revealed any obvious correlation with the incidence of peptic ulcer in this survey, but the figures so far are incomplete and final conclusions have not yet been reached.

Food factors.—The observations by Mellanby (1946) that flour treated by the Agene process caused hysteria in dogs raised the possibility that this or some other processing of food might be affecting the nervous system in man and indirectly lead to illnesses with a possible nervous factor, such as duodenal ulcer. This possibility has been carefully reviewed, but it appears that the process was not introduced into this country on an extensive scale until the early thirties and only became standard during the second world war, whereas the increase in duodenal ulcer took place during the twenties. Nevertheless, the possibility exists that an unrecognized toxic factor may be produced by modern methods of food processing. Gastric ulcer is common among the poorer classes and this could conceivably be due to different methods of cooking or to the consumption of more irritant foodstuffs. If duodenal ulcer is due to toxic factors in food it must be associated with something equally available to all sections of the community as there are no social differences in the incidence of duodenal ulcer. This aspect certainly deserves further study.

Psychosomatic factors.—There remains the possibility of a psychosomatic origin for peptic ulcer and there is much to suggest that the increase of duodenal ulcer may be due to the increase in the stresses and strains of modern life, which are being reflected in the stomach and duodenum. The increased number of perforations reported by Stewart and Winsor (1942) in London in the autumn of 1940, and by Illingworth, Scott and Jamieson (1944) in Glasgow in the spring of 1941, illustrate the close relationship between peptic ulcer and the stress of war. In a detailed study of 83 perforations and hæmatemeses, Davies and Wilson (1939) failed to find evidence of precipitating emotional stress in only one case. Few physicians will agree that psychic factors are as uniformly present as Davies and Wilson suggest, but all have had experience of individual cases in which emotional trauma has been repeatedly associated with hæmorrhage. Duodenal ulcer subjects, especially, are frequently of "the worrying type"; they brood over difficulties and worry inwardly. They are particularly sensitive and fussily tidy and therefore little things readily produce nervous tension. They are particularly conscientious and expose themselves to more difficulties than their easy-going fellow men. Frustration and resentment are two emotional states which particularly develop as a consequence of the interaction of their personality and the difficulties of the modern world.

dispose to ulcer formation as a result of the exposure of the mucosa to undiluted gastric juice for long periods at a time. This has been held to be the explanation of the assumed high incidence of ulcer among transport workers. Finally, occupation might be connected with psychosomatic factors, the responsibility and anxiety resulting from some forms of work being actively concerned with the development of duodenal ulcers in particular.

Occupational factors.—The literature on occupational differences in the incidence of peptic ulcer is conflicting. The most general view is summarized by Avery (1940) when he says: "The highly strung individual whose work involves a high pitch of nervous tension and worry, with irregular hours of work and irregular meal times is particularly liable to succumb to peptic ulcer. Amongst hospital patients, the incidence is highest among waiters, taxi drivers and transport workers, while in private practice, an unusually high proportion of medical men and women are seen." Hurst and Stewart (1929) found an unduly high proportion of ulcers among physicians, and Crohn (1927) and Ryle (1932) had similar impressions from their experience. In Alsted's (1942) and Ginannesschi's (1938) series the incidence of ulcer was high among professional and intellectual workers, but Ihre and Muller (1943) found that it was low. Schellong (1937) and Jennison (1938) reported a high incidence in building workers. Duesberg (1938) obtained a high incidence in foundry workers and labourers, whilst according to the Scottish Report on Incapacitating Sickness (Department of Health for Scotland, 1935) miners had a worse experience of peptic ulcer than the rest of the male insured population. In contrast, Ihre and Muller (1943) and Castrovilli (1937) found that the incidence in labourers was low. General agreement has only been obtained for two groups of workers, namely transport workers, in whom Ihre and Muller (1943), Sallstrom (1945), Ginannesschi (1938), and Castrovilli (1937) have all found high incidences, and agricultural workers, in whom the incidence has been commonly reported to be low (Ihre and Muller, 1943; Alsted, 1942; and Ginannesschi, 1938). By themselves none of the above reports are convincing as they are all open to major statistical criticisms, for example, sex differences have often, and age differences have nearly always, been neglected. However, in so far as they agree, they must be taken to provide presumptive evidence of occupational differences. By far the most convincing individual report is that of Schanke (1946), who has demonstrated a remarkable excess of gastric ulcers among the fishermen of northern Norway; he attributes this mainly to the extremely irregular meals which the fishermen are subject to in the course of their work.

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INSTRUCTIONS FOR THE PATIENT WITH DYSPEPSIA*

By C. M. FLETCHER, M.D., F.R.C.P.

THERE is a common belief among the laity that doctors are initiated, during their long training, into the magic of chemical transformations, into rites of death and potions of life, and develop a mysterious omniscience in which the untrained cannot share. "My doctor says . . ." is often a prelude to a statement that is considered almost oracular. The common belief in these mystical powers is of great importance to some practitioners. For them the idea that a patient may not only understand but even undertake a part of his own treatment is a dangerous heresy, the acceptance of which might lessen the efficacy of the many placebos with which his therapeutic regimes abound. There was perhaps some justification for this esoteric attitude some thirty or more years ago when the physician had almost no specific and effective remedies to prescribe, but now that the laboratory worker has provided him with real therapeutic power he has no longer such need to rely on mystery and he may often, and with benefit, lead his patients towards considerable understanding of the nature of their maladies and the purpose of their remedies. There is usually no need for a patient to understand the nature of acute and transient illnesses, except in so far as his curiosity may lead him, but in chronic and recurrent conditions, when treatment may have to be prolonged or repeated, much may be gained by training the patient to understand his symptoms and their treatment so that he may manage them without constant recourse to medical advice.

THE NEED FOR THE PATIENT'S COOPERATION

The advantages of such understanding are perhaps best seen in cases of diabetes mellitus, in which the training of the patient in the management of his diet, his varying insulin requirements, his hypoglycæmic reactions and so forth, is an essential part of successful treatment. Similar advantages may also accrue to the chronic dyspeptic whose symptoms, whilst recurrent and troublesome, are not so severe as to warrant a surgical operation. It is not suggested that either the diabetic or the dyspeptic should cast medical advice on one side and become his own amateur medical adviser. The initial diagnosis and prescription of the appropriate regime must be in the hands of an experienced physician. From the outset, however, the

* For the convenience of practitioners the second section of this article (pp. 53-60) entitled "Notes on the Nature and Treatment of Indigestion" is available in pamphlet form suitable for distribution to patients. For particulars see page 88 of this issue.

It is probably a fair comment that the day-to-day stresses of life have increased in the past thirty years and this may yet prove to be responsible for the increase in duodenal ulcer.

The results of the occupational survey mentioned previously are consistent with a psychosomatic basis for duodenal ulcer. There was a definite correlation between "anxiety at work" and the frequency of duodenal ulcer. Managerial posts, carrying responsibility and its resultant worries, provided an undue proportion of duodenal ulcers. The agricultural worker, possibly more philosophical and phlegmatic, revealed a marked deficiency of duodenal ulcers.

CONCLUSION

Peptic ulcer remains an unsolved problem but the pieces of the jigsaw are gradually being found, and further study of environmental and psychological factors should bring others to light.

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NOTES ON THE NATURE AND TREATMENT OF INDIGESTION

WHAT IS INDIGESTION?

During digestion, the food we eat is broken down into simple substances which can be dissolved in the blood. They are then taken by the circulation to the various parts of the body where they are needed for growth or healing, or simply for providing energy and warmth to maintain life.

When a mouthful of food is swallowed, it passes down the gullet into the *stomach*, which is like an elastic bag. This is where digestion begins: the food is mixed with digestive juice and becomes softened before passing on into the first part of the gut which is called the *duodenum* (its name comes from the Latin for twelve—*duodecimus*—because it is about twelve finger-breadths in length). Here it is mixed with bile from the liver and with digestive juice produced by the pancreas (sweetbread). It then goes on into the rest of the gut where digestion is completed and the digested

food is absorbed into the blood to be carried all round the body. In the stomach the digestive juice is acid (about as acid as vinegar), but in the duodenum the acid is neutralized by alkali from the pancreas.

Normally your stomach does not digest itself! This is rather remarkable when you think that if you eat a piece of tripe, which is sheep's stomach, it is digested away perfectly easily. The healthy stomach and gut have some means, which we do not completely understand, of protecting themselves against the action of

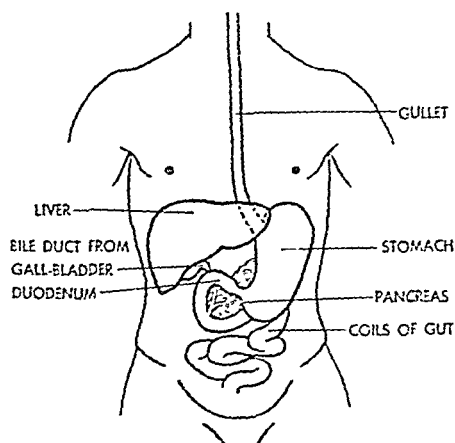


Diagram of stomach and duodenum..

their own digestive juices. When you have indigestion this self-protection may fail, as we shall see.

WHAT IS "INDIGESTION"?

The symptoms of indigestion are pain or discomfort in the neighbourhood of the stomach or the lower part of the chest and sometimes in the back, before or after taking food or drink. There may also be belching and repetition or even vomiting of food which may ease the pain. These symptoms are not actually due to the food failing to get digested, but they are due to some sort of soreness or inflammation of the lining of the stomach or duodenum. This is made worse by the acid in the stomach juice, which does not hurt a healthy stomach, but which may hurt if the stomach lining is already sore. That is why the pain may be eased by taking alkali (such as

patient should be given an insight into the rationale of his treatment, and should, from then on, feel himself to be a pupil and ultimately a collaborator with his doctor in intelligent and careful management and follow-up of his case. Thus he will be able, on his own account and for long periods, to make such alterations and adjustments in his regime as the changing circumstances of his case may demand. It should, however, be made clear to him that the occurrence of new symptoms or the failure of old symptoms to respond to accustomed treatment should always be the occasion for seeking further advice from his doctor.

If this thesis be granted, there remains a serious practical problem, and that is the means by which the patient is to receive the instruction that he needs. The practitioner has no time to give each dyspeptic patient a long discourse on his condition and its management, nor is it usually possible to muster a group of patients for a lecture. It is because of this difficulty, more than because of the doctor's desire to retain mysterious authority, that the majority of patients with indigestion are given such scanty instructions concerning the nature of their illness and the reasons underlying the regime that they need to follow. The solution can only lie in the provision of a pamphlet, simple but thorough, which the patient may be given to read. On his subsequent visits to the doctor he must be encouraged to ask questions on any points that remain obscure, for no pamphlet, however well designed, can suit every case or every level of intelligence. Even if many questions have to be answered, the time and effort spent by the practitioner on each case will be far less than if he had to carry out the whole instruction verbally.

The following pamphlet is an attempt to explain in simple language the principles and practice of the treatment of dyspepsia. It is hoped that its use may be found of value, either unmodified or modified to suit the particular therapeutic inclinations of individual practitioners.

Before presenting the pamphlet, however, it is necessary to make clear what is meant by the term dyspepsia. It may be defined as painful gastric or duodenal dysfunction, whether due to peptic ulcer or to other causes. The clinical picture consists of epigastric pain or discomfort which bears a definite temporal relationship to the taking of food or milk, being either relieved or exacerbated by it, and which is relieved, at least to some extent, by alkali. This simple diagnostic rule should make it possible to avoid treating as dyspepsia a pain due to arthritis of the spine, fibrositis, cholecystitis, disease of the intestine, or thoracic disease. A more precise diagnosis than that of "dyspepsia" is usually necessary for successful treatment, but the means by which this precise diagnosis may be reached will not be discussed here. The pamphlet is intended solely for those cases in which a dietary regime suitable for peptic ulcer is required, whether the diagnosis is in fact peptic ulcer or inoperable cancer, "postoperative stomach", "gastritis", or dyspepsia of uncertain origin.

but this is where you are wrong. An empty stomach may start to digest itself, particularly when it is active during the day. So *take a snack* (see p. 59) *at least every two hours* during the day, and at night if you wake.

(3) *Avoid big meals.*—Big meals over-fill the stomach and irritate it: “*little and often*” should be your motto.

(4) *Eat slowly and chew thoroughly.*—If you hurry your meals you cannot chew properly. Unchewed lumps of food irritate the stomach and take a long time to soften. Meals must be eaten slowly and every mouthful must be completely softened by chewing before it is swallowed. If your teeth are not good you cannot chew properly and you should go to your dentist to have them put right or to have false ones fitted. Some foods are difficult to chew up even with perfect teeth. They are given in the list of “indigestible foods” (p. 60) and should be avoided.

(5) *Avoid stimulants.*—Tobacco, strong tea, coffee and alcohol all stimulate and irritate the stomach. *Stop smoking.* If you cannot stop completely, then only smoke after a main meal. *Avoid alcoholic drinks* of all kinds, especially on an empty stomach. *Tea* should only be taken with plenty of milk. *Coffee* is best avoided, but may be taken very weak, with plenty of milk. You should also avoid strong seasoning, pickles and spices and, of course, any particular foods which you have found from experience are liable to upset you.

Details of three diets are given later: a very strict one (No. 1), a moderately strict one (No. 2), and a generous or convalescent one (No. 3).

When you start dieting your doctor will tell you which diet to take and he will give you a priority card which will enable you to get the extra milk and eggs that you will need. In general, No. 1 is for those who have much vomiting or severe pain. No. 2 is for those with considerable pain but little vomiting. No. 3 is for those with only mild pain or discomfort.

Increases in diet should be taken on your doctor's advice. *Any increase should be slow and gradual*, the stricter diets being modified by the inclusion of items from the fuller diet one by one.

Return to normal diet.—Indigestion pains disappear long before the actual inflammation has gone or the ulcer has healed. You should not take a normal diet until your ulcer (if you have had one) has been healed or you have had no indigestion for at least six months. However, you should always avoid the most indigestible foods (listed below) and anything else which you personally find indigestible.

If you have a return of pain, you should do two things:—(1) Try to discover what has upset you. It may be something you have eaten or it may be worry, or indulgence in a “stimulant”. Avoid it in future. (2) Go down a step on the diet scale (i.e., if you are on a normal diet, take diet 3, or if you are still on diet 2, take diet 1 and so on) for a few days and rest as much as possible. If the pain goes, gradually increase your diet over a period of a few weeks. In this way you may prevent a slight return of indigestion developing into an ulcer. If the pain persists, consult your doctor.

bicarbonate of soda or magnesia) which neutralizes the acid, or by vomiting, which empties the stomach of the acid. A sore stomach works badly and often fails to empty, so that it gets overfilled, and this is what leads to vomiting.

In some cases, if the inflammation continues and gets worse, the lining may lose its power of resisting digestion and an ulcer or sore may form. These ulcers only form in the presence of acid, that is, in the stomach or in the first part of the duodenum before the acid has been neutralized. If the inflammation still continues, the ulcer may get bigger and deeper, and more serious complications may follow. Fortunately, these complications are rare.

The ulcer may "perforate", which means that the stomach or duodenum gets digested right through in one place so that food and digestive juice escape through the hole into the inside of the abdomen. This causes sudden, extremely severe pain, and it is necessary for an operation to be performed as soon as possible to sew up the hole.

The other complication is when a blood vessel is digested away. If this happens a hæmorrhage occurs and blood may either be vomited or passed by the bowel, when the motions appear black and shiny like tar. If the hæmorrhage is severe the patient may faint, and in some cases blood transfusion is necessary.

So you see how important it is to *treat indigestion early*, before an ulcer has formed, and you can also see that once an ulcer is formed, really strict treatment is necessary in order to avoid serious complications. The objects of treatment are to rest and soothe the stomach so that the inflammation may get better, and to protect it against its own digestive action until it has regained its natural powers of resistance. In a few cases these simple methods fail and it may then be necessary to do an operation to remove the ulcer and part of the stomach that produces acid. But this should seldom be necessary if indigestion is properly treated before it has become too bad.

There are four main lines of treatment for indigestion:—

- (1) Taking a suitable diet
- (2) Taking medicines and powders
- (3) Rest for the mind
- (4) Rest for the body

DIET

The object of dieting is to give the stomach the sort of foods it can handle most easily and to avoid habits which upset it. Here are the rules:—

- (1) *Have regular meals.*—Your stomach likes regular hours. It is used to being filled with food at the usual meal-times. It prepares for these expected meals in advance: it becomes active, and produces digestive juice and acid in readiness. If the meal is delayed you may get pain and the stomach may begin to injure itself. So *be regular and punctual in your main meal-times.*
- (2) *Have frequent "snacks".*—Food (and remember milk is the best of foods) temporarily neutralizes the acid in the stomach. That is why indigestion pains are sometimes eased by meals or snacks. You may think you should rest your stomach by eating little or nothing if you have indigestion,

but this is where you are wrong. An empty stomach may start to digest itself, particularly when it is active during the day. So *take a snack* (see p. 59) *at least every two hours* during the day, and at night if you wake.

(3) *Avoid big meals.*—Big meals over-fill the stomach and irritate it: “*little and often*” should be your motto.

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If you have a return of pain, you should do two things:—(1) Try to discover what has upset you. It may be something you have eaten or it may be worry, or indulgence in a “stimulant”. Avoid it in future. (2) Go down a step on the diet scale (i.e., if you are on a normal diet, take diet 3, or if you are still on diet 2, take diet 1 and so on) for a few days and rest as much as possible. If the pain goes, gradually increase your diet over a period of a few weeks. In this way you may prevent a slight return of indigestion developing into an ulcer. If the pain persists, consult your doctor.

MEDICINES AND POWDERS

Medicines may be very useful for indigestion, but should only be taken on the advice of your doctor. They may be used to neutralize acid, to soothe the stomach, to supplement a strict diet, or to help you sleep.

(1) *Antacids*.—These are usually white powders, tablets, or medicines containing various sorts of alkali to neutralize acid in the stomach. Some of them (especially bicarbonate of soda) may be harmful if taken in large quantities over a period of weeks or more. Your doctor will tell you whether you should take them at all, and in what quantities and how often. If one sort does not ease you or if it affects your bowels, ask him to try a different mixture. The best rule is to take alkalis *between* meals and snacks when you have pain or discomfort, but some people prefer to take them immediately after meals.

(2) *Belladonna* and *olive oil* may soothe the stomach and may be advised by your doctor.

(3) *Vitamins*.—A diet that is suitable for indigestion may contain very few vitamins, so your doctor may advise you to take vitamin tablets or fruit juice. Do not forget to take them; they may be very important in speeding your recovery.

(4) *Sedatives*.—These may be useful if you are worrying or are not sleeping well.

REST FOR THE MIND

Everyone knows that sudden fear or a shock can affect the stomach. People talk of being "sick with fright" or say their "stomach turned over", and it is a fact that the working of the stomach may be upset by fear. Sudden frights do no serious harm, for they are soon over, but continuous mental strains, anxieties, frustrations or resentments, even though they are small in themselves, combine to keep the stomach in a state of irritation which may lead to symptoms of indigestion, and even to an ulcer.

People who get indigestion are often of a worrying, sensitive type, even though they would hate to admit it. Perhaps you do not think you are, for you may keep a firm grip of yourself. Just ask yourself these questions and give an honest answer:—

Do you turn little worries over and over in your mind, although you try to appear calm and unconcerned?

Do you brood over bad luck, or when you feel you have been "done"?

Do you resent criticism or worry about what people think of you?

Do people "get on your nerves" easily?

Do you have to drive yourself all day because you have really got too much to do, so that you are always "on the go" and cannot relax?

Are you usually dissatisfied with yourself so that you are always striving to do "one better"?

Do you feel people do not understand or appreciate you enough?

If you must honestly answer "yes" to more than one of these questions, then mental strain is probably playing a part in upsetting your stomach.

There is nothing to be ashamed of in this. Indeed the most valuable people are often those who drive themselves into doing or worrying about more than they can really manage. *But*, if you are to do your job properly, you must give your stomach a chance. So *you must learn to slacken off your stresses and strains*. Stop turning things over and over in your mind. Laugh it off if you are offended or ticked off, or if people annoy you: do not let them get a rise out of you.

See if you cannot get a chance to rest and relax your mind occasionally during the day. This may mean giving up some of your activities, or handing over some responsibilities, but it is better to do fewer things well than to do a lot of things badly because you are unwell, or to have to go to bed and do nothing at all for a while.

Many people have proved for themselves the truth of the text: "Thou shalt keep him in perfect peace whose mind is stayed on Thee." You may well seek and find the peace of mind that you need from this Source.

If you have any special worries, talk them over with a sensible friend. If you still go on worrying and feeling on edge, tell your doctor. He may be able to help you and, if necessary, he may give you medicine to settle your nerves and help you to sleep. He may also be able to advise you whether you should not arrange your work differently on medical grounds.

REST FOR THE BODY

We have seen the importance of rest for your mind; but what about rest for your body? This is very important, too. When you take exercise your muscles need more blood to circulate through them. They get it at the expense of the rest of the body, and particularly at the expense of the stomach. So you must avoid taking exercise either just before or just after meals. *Sit still and relax for at least a quarter of an hour before and after your main meals* and let your stomach do its job in peace. If your indigestion is really bad it is best to go to bed for a time. Nothing will stop indigestion pains more quickly than going to bed for a complete rest. Your doctor will advise you how long you need to stay in bed. If you have had an ulcer you may need to stay in bed long after the pain has gone, until the ulcer is really healed.

Really sound sleep is most important for anyone with indigestion. A restless night is as bad for your stomach as an anxious day. You may need medicine or tablets to help you sleep. They are quite harmless, and are not dangerous drugs if used sensibly under medical direction, so do not hesitate to take them. If you are not sleeping well, ask your doctor to give you something to help you get a really good night's sleep.

Anticipation.—Forewarned is forearmed. If at any time you know you are going to have an unavoidable time of anxiety, worry or overwork, it is wise to anticipate a possible return of indigestion by going on to a stricter diet, taking powder or medicine regularly (if your doctor prescribes them),

and resting whenever possible—going to bed early and even spending week-ends in bed.

ESSENTIALS

To sum it all up, then: to treat and avoid indigestion you need:—

- (1) A suitable diet, with regular, frequent, small, unhurried meals.
- (2) No smoking or other stimulants.
- (3) A calm mind and time to relax.
- (4) Sound sleep.

If you can manage all this, your stomach will get well and stay well.

DIET FOR INDIGESTION

DIET 1 (STRICT)

(If you need this diet you should rest at home, preferably in bed)

6 a.m. (If awake) 5 oz. (small breakfastcup) of milk.

8 a.m. 5 oz. of custard mixture.*

10 a.m. 5 oz. of milk.

12 noon 5 oz. of custard mixture.

2 p.m. 5 oz. of milk.

4 p.m. 5 oz. of custard mixture.

6 p.m. 5 oz. of milk.

8 p.m. 5 oz. of custard mixture.

10 p.m. 5 oz. of milk.

At night (if awake) 3 oz. of milk.

All feeds should be taken warm (not hot).

If you are thirsty, you may drink plain water in small quantities between the feeds.

Between each feed (i.e., at 7, 9, 11 a.m., 1, 3, 5, 7, 9 p.m.) and at night if you wake, take a level teaspoonful of alkaline powder, or a dose of medicine *if prescribed by your doctor*.

If you are troubled by *vomiting*, the milk should be diluted half and half with water and only 3 oz. taken at each feed.

If you have no vomiting and your pain rapidly improves, take two plain biscuits or two small pieces of crisp toast, buttered when cold, at 10 a.m., 2 p.m., and 10 p.m., with the 5 oz. of milk. If you continue to improve, take a little strained porridge or patent cereal baby food at 8 a.m. and a small helping of pudding at 12 noon and 8 p.m., for two or three days before starting Diet 2.

Extra nourishment can be obtained by adding a teaspoonful of sugar to each feed. This should be done if the diet is taken for more than two days.

The milk feeds may be flavoured with a little cocoa or Ovaltine, Bournvita, Horlicks or Marmite, or the milk may be taken in the form of junket.

Vitamin C tablets, blackcurrant purée, or rose-hip syrup should be taken as prescribed by your doctor.

**Custard mixture* should be prepared for the day by stirring two eggs (fresh or reconstituted dried) into 16 oz. of milk. Before taking the mixture, warm it to thicken. Flavour with vanilla or chocolate if desired. If you cannot get enough eggs to make the custard mixture you may use either a proprietary brand of "strained custard pudding" or, better still, make a "fortified milk mixture" by adding 2 oz. of dried milk powder to 1 pint of milk.

DIET 2 (MODERATE)

6 a.m. 5 oz. of warm milk.

8 a.m. Small helping of patent groats, patent barley, or strained porridge made with milk. Bemax may be added.

Two slices crisp toast, buttered when cold.

One lightly boiled or poached egg, or scrambled dried egg.

5 oz. milk flavoured with weak tea.

Jelly, honey or syrup.

- 10 a.m. 5 oz. warm milk.
 12 noon Small helping steamed fish or egg as at 8 a.m.
 Two slices crisp toast, or plain biscuits with butter.
 Small helping of pudding.
 5 oz. of milk (including that used in pudding).
 (Add small helping creamed potato after one week on Diet 2.)
 2 p.m. 5 oz. of warm milk or milk pudding (e.g. junket, egg custard or cornflour).
 4 p.m. 5 oz. of milk with weak tea.
 Two slices crisp toast, or biscuits, with butter.
 Small slice plain cake.
 Jelly, syrup or honey.
 6 p.m. 5 oz. warm milk or cream of vegetable soup.
 8 p.m. Same as at 12 noon.
 10 p.m. 5 oz. of warm milk.

The times may be varied to suit you so long as the intervals between feeds are not longer than 2½ hours.

Sugar or glucose may be taken as desired.

If thirsty, water or fruit juice may be taken as desired, but not more than 5 oz. at a time.

The milk feeds may be flavoured with a little cocoa, Ovaltine, Bournvita, Horlick's or very weak tea, or they may be taken in the form of junket.

Vitamin C tablets, blackcurrant purée, or rose-hip syrup should be taken daily as prescribed by your doctor.

Powder or medicine should also be taken as prescribed by the doctor.

DIET 3 (CONVALESCENT)

Breakfast : Cornflakes, patent groats or barley, or strained porridge with Bemax and 5 oz. of milk.

Lightly boiled, poached or scrambled (shell or dried) egg.

Bread or toast and butter.

Weak, milky tea.

Honey, syrup or jelly.

Dinner : Boiled, steamed, baked or grilled white fish, soft roes, tripe, brains, sweetbread, chicken or rabbit. White sauce. (Lamb, tender beef or liver—minced if possible—if your doctor advises it.)

Mashed potato.

Soft parts of well-cooked root or green vegetables (sieved if possible) or cauliflower.

Pudding (see list).

Bread or toast and butter.

Tea : Bread or toast and butter.

Plain cake or biscuits.

Milky tea.

Honey, syrup or jelly or peanut butter.

Supper : Boiled or steamed fish, egg as at breakfast, or grated cheese.

Bread or toast and butter.

Sieved vegetables.

Milk (with weak coffee, tea, cocoa or Ovaltine) or milk vegetable soup.

NOTE.—The bread should not be new. The toast should be crisp and buttered when cold.

In addition to these four main meals, take one of the following snacks in the intervals between them, before going to bed, and if you wake at night, so that you never have more than two hours during the day without taking something.

SNACKS

Small cup of milk (flavoured with weak tea, very weak coffee, Ovaltine, Bournvita, cocoa or Horlick's, if desired), or

½ oz. of plain or milk chocolate, or

2 or 3 tablets of Horlick's malted milk or Ovaltine, or
2 plain biscuits or slices of crustless bread with butter and jam or paste, or
slice of plain cake.

Vitamin C and medicine should be taken as in Diet 2.

SUITABLE PUDDINGS

Junket, well-cooked rice, ground rice, cornflour, semolina, tapioca, vermicelli, arrowroot. Flavour with coffee, chocolate, caramel, almond or vanilla.

Milk jelly. All other kinds of jelly.

Custard, baked or boiled.

Blancmange.

Steamed sponge or castle puddings.

Fruit fool.

Sieved stewed apples, pears, prunes, plums.

Sweet omelette.

Queen of puddings, meringues, ice cream, trifles, sieved apple charlotte.

INDIGESTIBLE FOODS TO BE AVOIDED

Meat soups and extracts.

New bread.

Coarse biscuits, e.g. digestive, oatmeal, etc.

Fish with fine bones.

Fried foods of all kinds.

Pastries and suet puddings.

Pickles and spices, vinegar, curries, pepper.

Raw vegetables and fruits, salads, onions.

Reheated and "made up" dishes.

Sausage.

Jam with pips, seeds or skins.

Fruit cake.

Nuts.

Coffee or strong tea.

Anything (even if it is included in the diet) that you personally find indigestible.

MEALS AWAY FROM HOME WHILE AT WORK

If you can get home for a peaceful midday meal without hurrying or undertaking a tiring journey, you should do so. If you cannot do this, there are three alternatives:—

(1) *Get the meal at an invalid kitchen.* Ask the Welfare Worker at work or at the hospital if one is available.

(2) *Take sandwiches with you.* These should be made with crustless bread (not new). Suitable fillings are:—

Grated or processed cheese.

Scrambled dried or shell egg.

Tinned salmon.

Meat or fish paste.

Spam.

Pilchards or sardine.

(3) *Have a small helping of suitable dishes at a local canteen or restaurant such as:—*

Thick vegetable soup.

Mashed potatoes and gravy.

Omelette or other egg dish.

Macaroni cheese (avoid skin).

Spaghetti or baked beans on toast.

Plain tripe.

Minced lamb, mutton, chicken, rabbit.

Well-cooked fish.

Tomato purée or Marmite as flavouring.

Sieved prune.

Chocolate spread.

Peanut butter.

Boiled fish.

Suitable pudding (see list).

Bread, butter and cheese.

Jelly or seedless jam.

Plain minced meat (cottage pie, etc.).

THE DIETETIC TREATMENT OF OBESITY

By IAN A. ANDERSON, M.B.E., M.B., B.Sc.

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DESPITE a considerable volume of research on the subject, the pathogenesis of obesity is still somewhat of a mystery. It cannot be denied that, in the final analysis, obesity of any sort is the result of an intake of energy that has exceeded the output. It is now well established that in the vast majority of obese patients the total metabolism is at least as great as that of normal persons, so that the positive energy balance that produces the obesity must be due to overeating. Just what impels the candidate for obesity to eat more than his energy expenditure demands is still a matter of controversy. Conscious gluttony explains only a small minority of cases, but some hold that the obese differ from normal persons only in that faulty training in childhood, bad habits in the selection of food or some effect of emotion on appetite have led to overeating. A few investigators, whilst admitting that the obese must have overeaten to become fat, consider that they have been impelled to do so owing to an abnormal tendency of their subcutaneous tissue to store fat and resist its subsequent mobilization, which causes undue diversion of food fat to the fat depots.

Overeating and obesity can be produced in laboratory animals by experimental lesions in the hypothalamic region of the brain. The possible significance of this finding in the causation of obesity in man cannot be overlooked, although so far no evidence has been adduced that obesity is due to removal of the inhibitory control that the hypothalamus seems to exert on the hunger mechanism.

The pathogenesis of obesity cannot be dismissed without a brief reference to the vexed question of "endocrine" obesity. This once popular diagnosis is now realized to rest on very slender foundations, and it is generally agreed that endocrine influences are on the distribution rather than on the total amount of body fat. It is true that a certain small proportion of cases of obesity may show clinical manifestations suggesting disordered endocrine function, but when recognizable endocrine disease is associated with obesity such disease should be considered as an additional diagnosis, not as the causal factor of the obesity.

REGULATION OF METABOLISM

With no clue yet revealed as to the pathogenesis of obesity, reliance must still be placed on the time-honoured method of treatment, namely the imposition of a negative energy balance, to counteract which the body must draw on its fat stores. Theoretically, there are two ways of securing this negative energy balance—by reducing the energy intake and by increasing the energy expenditure. In practice, the latter is much the less important

and can be dismissed briefly. *Physical exercise* has obvious limitations in the obese, especially in the presence of the locomotor disabilities, such as arthritis, flat foot and varicose veins, that are such common complications of obesity. Besides, the amount of energy expended in mild physical exertion is less than is often believed.

Thyroid hormone has long been used in the treatment of obesity for its stimulating effect on energy metabolism. Modern opinion is against its indiscriminate use for this purpose. It is now known that the energy expenditure of obese patients is at least as great as that of normal persons, so that any increase induced by thyroid hormone is in the nature of a toxic effect. Administration of thyroid hormone in obesity should be limited to two groups of cases:—

(1) The very small minority of patients who show clinical manifestations of hypothyroidism and have a significantly lowered basal metabolic rate.

(2) Obese patients who have lost weight on a reducing diet for some time, but have then reached a plateau of weight still well above normal in spite of strict adherence to diet. This phenomenon is due to a lowering of basal metabolism from undernutrition so that the reducing diet is no longer an effectively sub-maintenance one. Small doses of thyroid at this stage may tip the balance in favour of weight loss again.

PRINCIPLES OF DIETARY RESTRICTION

All the emphasis in the treatment of obesity must therefore be placed on the consumption by the patient of a reducing diet. This diet must conform to the following criteria:—

(1) Its energy content must be sufficiently less than the patient's energy expenditure to produce a progressive loss of weight, but at a rate that does not leave the patient exhausted and weakened.

(2) Nitrogenous equilibrium must be preserved by the inclusion of an adequate amount of protein—ideally at least 1 g. per kg. of ideal body weight.

(3) The diet must contain sufficient bulk to satisfy the patient physically, so far as possible, and so prevent undue suffering. It must be admitted, and the patient should be warned accordingly, that successful weight reduction always entails some discomfort in the way of unsatisfied appetite, and that resolution on his part in keeping to the prescribed diet is an essential factor in successful treatment.

(4) The diet should be constructed so as to meet the mineral and vitamin requirements, as it must be continued over a period of at least some months.

Before attempting to lay down a dietary regime a searching inquiry must be made into the patient's previous food habits. This may bring to light some abnormal method of eating, such as the over-ingestion of a particularly energy-rich food or indulgence in between-meal snacks. Correction of such indiscretions may be sufficient to effect improvement in mild cases of obesity. But in a case of any severity it will be necessary to prescribe a rigid diet.

The precise level of caloric intake that should be allowed will vary somewhat according to the degree of obesity and the age and physical activity of the patient. It is generally agreed that better results are obtained by a moderate reduction in calories than by intensive cures with such severe caloric restriction that they can only be continued for a few weeks, during which the patient has to be kept in bed. The usual practice is to reduce the energy intake to about 50 per cent. of the maintenance caloric requirement at the patient's "ideal" weight. In general, this means a diet of about 1200 calories for a man and 1000 calories for a woman.

The rate of weight loss to be aimed at is about two pounds (1 kg.) per week. In the rare instances when this rate is exceeded for any length of time the diet should be increased by 100 calories every two weeks until the desired rate of weight loss has been achieved. It is much more common to find that the weight does not fall at the expected rate and may even show no decrease over the first week or two. If it can be proved that the patient is in fact keeping to the prescribed diet, the failure to lose weight is to be ascribed to temporary water retention in the tissues, a phenomenon seen in normal, as well as in obese persons, when subjected to a diet of inadequate energy value. This excess fluid will be eliminated ultimately, but water and salt restriction (i.e., not more than two pints (1 litre) of fluid as such in the day, no salt to be added to food at table and no very salty food such as preserved meat included in the diet) is advantageous, especially in the first few weeks of treatment. It minimizes the masking effect of water retention on the actual loss of body substances, which discourages a patient who may be observing meticulously the dietary restrictions imposed on him.

Translation of the principles enumerated above into a practical diet calls for a relatively large meat or fish intake to preserve nitrogenous equilibrium and promote satiety, and a generous ration of fruit and vegetables to give bulk with minimal energy intake. The present difficulties with regard to both these demands needs no emphasis, and the provision of a practicable reducing diet is a sore tax on the ingenuity of the dietitian in these days of scarcity.

DIETARY REGIME

The specimen 1000 calorie diet given at the end of this article is a compromise designed to meet present-day conditions by keeping within the allowances of rationed food and yet, it is hoped, providing sufficient alternatives to allow a patient to follow it without undue difficulty.

The diet contains about 60 g. of protein—not as much as would be desirable but certainly enough to maintain nitrogenous equilibrium. The mineral and vitamin contents should be adequate, with the possible exception of the vitamin B₂ complex. This deficiency in what is to be a long-term diet should be made good with some of the proprietary preparations containing the B₂ complex, e.g. "benerva" compound (Roche), one tablet per

day; "beplex" capsules (Wyeth), three tablets per day. If a diet of more than 1000 calories is to be prescribed, this can be done by adding the required number of 100 calorie portions of foodstuffs given in note 5 (p. 66). Bread and potatoes are preferable to butter, bacon or jam on account of the relatively high energy value and lack of bulk of the latter. But the inclusion of bacon or jam on one or two days in the week helps to vary the monotony of the diet and so aids the patient's resolution to keep to it.

The patient should be made to weigh all the restricted articles of food in the early weeks of treatment. This emphasizes the paramount importance of diet in his treatment, and he should only be allowed to measure his rations by the eye when he has served a considerable apprenticeship at the weighing scales. The patient himself should not be weighed more often than once a week—more frequent weighings tend only to discourage him.

DRUGS

A comparatively recent adjunct to the dietary treatment of obesity is the use of drugs of the amphetamine series—"benzedrine" (amphetamine sulphate) or more recently "dexedrine" (dextro-amphetamine sulphate)—to depress the appetite. It is claimed for these drugs that besides depressing appetite, their stimulant effect on the central nervous system eliminates the sense of depression and irritability that often accompanies adherence to a strict low-calorie diet. Dexedrine is preferable to benzedrine in its comparative lack of peripheral side-effects and, provided that it is not given to patients with hypersensitivity to ephedrine-like compounds, anxiety states, or cardiovascular disease including hypertension, it is worthy of trial in patients who find difficulty in adhering to their diet or who suffer depression or irritability owing to the caloric restriction. It is recommended that the drug should be given in small doses initially, say, 2.5 mg. thrice daily, i.e., before breakfast, before lunch and not later than 4 p.m. (to avoid insomnia). If this dose is ineffective it should be increased up to a maximum of 5 mg. thrice daily.

Many favourable reports have been published on the use of the amphetamine drugs in the treatment of obesity. But a somewhat pessimistic note has been sounded in others, where it is suggested that appetite-reducing drugs are effective only in patients who have sufficient resolution anyway to restrict their diet, and that patients who cannot resist the drive of appetite are also resistant to the action of these drugs.

LATE RESULTS OF TREATMENT

Most physicians will admit that the end-results of the treatment of obesity are often disappointing—a not unexpected outcome when it is remembered that weight reduction by diet is not attacking the underlying factor, whatever it is, that drove the obese patient to overeat. Therefore even when a success-

ful degree of weight reduction has been achieved, continued supervision of the patient's eating habits is necessary if a relapse is to be avoided. He should be placed on a diet that supplies about the maintenance caloric requirement at his "ideal" weight, which, roughly speaking, is about 2500 calories for the average man and about 2000 calories for a woman, or a little more if much physical exercise is being undertaken. Space forbids the inclusion of a separate maintenance diet, but addition of the following items will increase the energy value of the 1000 calorie diet to about 2000 calories:—

Butter, margarine, or fat	$\frac{1}{2}$ ounce	= 110 calories.
Bread	5 ounces	= 350 calories.
Potatoes	10 ounces	= 210 calories.
Jam	$\frac{1}{2}$ ounce	= 35 calories.
Buns, cakes, etc.	3 ounces	= 270 calories.
Sugar	$\frac{1}{2}$ ounce	= 55 calories.

Only by continued attention to his diet will the obese patient who has undergone a successful reduction cure overcome the underlying drive to overeating and so prevent a relapse to his former obese state.

SPECIMEN 1000 CALORIE OBESITY DIET

Breakfast

One egg, boiled or scrambled.
 or Sausage—small serving ($1\frac{1}{2}$ ounces).
 or White fish, steamed—average serving (3 ounces without bone).
 or Finnan haddock—average serving (4 ounces).
 or Herring, baked—small serving ($1\frac{1}{2}$ ounces).
 or Herring, kippered—small serving (2 ounces with bone).
 or Porridge made from $\frac{3}{4}$ ounce oatmeal, with milk from daily ration.
 or Wheatflakes, $\frac{3}{4}$ ounce, with milk from daily ration.
 Bread—two thin (1 ounce) slices, preferably wholemeal.
 Butter from daily ration.
 Tea, with milk from daily ration.

Forenoon

One small apple or orange.
 or One water biscuit, and tea with milk from ration.

Lunch

Clear meat soup, with no thickening of flour, and no barley, peas or beans, but with other chopped vegetables if desired. Quantity as desired up to a maximum of 10 ounces.
 Lean meat, with all visible fat removed—small serving ($1\frac{1}{2}$ ounces).
 or White fish, steamed or baked—average serving (3 ounces without bone).
 or Corned beef—small serving ($1\frac{1}{2}$ ounces).
 or Offals (kidney, liver, tripe)—average serving (3 ounces).
 or Rabbit, stewed—average serving (3 ounces with bone).
 or Chicken, boiled—small serving (2 ounces without bone).
 or Sausage—small serving ($1\frac{1}{2}$ ounces).
 Boiled vegetables—greens, carrot, turnip, celery, cauliflower, French beans, or vegetable marrow—large serving, i.e., as much as desired.
 or Salad, made from lettuce, tomato, spring onion, or cabbage, but excluding potato and peas—large serving.
 Fruit, fresh or stewed—average helping. (N.B., no tinned stewed fruit).

or Junket, made with milk from ration.

or Milk pudding made with $\frac{1}{2}$ ounce cereal and milk from ration.

Tea

Bread—one thin (1 ounce) slice.

or Bun—one small.

or Water biscuits—three.

or Rich tea biscuits—two

Butter from daily ration.

Tea, with milk from daily ration.

Supper

White fish, baked or steamed—average serving (3 ounces without bones).

or Cheese, $\frac{3}{4}$ ounce.

or Lean meat, with all visible fat removed—small serving (1 $\frac{1}{2}$ ounces).

or Any of the alternatives for 1 $\frac{1}{2}$ ounces lean meat given under "Lunch".

or One egg.

or Any of the alternatives for one egg given under "Breakfast", except for porridge and wheatflakes.

Boiled vegetables (as at lunch)—average serving.

or Salad (as at lunch)—average serving.

or Boiled potatoes—small serving (2 ounces).

Bread—two thin (1 ounce) slices, preferably wholemeal, with butter from daily ration.

or Boiled or baked potatoes—average serving (5 ounces).

Daily Rations

Butter or vitaminized margarine— $\frac{1}{2}$ ounce (approximately four small pats with the diameter of a sixpence).

Milk, whole—8 ounces.

or Milk, whole—2 ounces; and milk, skimmed—10 ounces.

Vitamin B supplement.

Notes

(1) Mineral oil (liquid paraffin) and lemon juice or vinegar may be used to make salad dressing.

(2) No sweet wines, spirits, beer, sweetened aerated waters or fruit cordials to be drunk.

(3) If hunger is troublesome, the patient should eat more vegetables.

(4) No fried foods, pastries, tinned fruit, sweets or preserves to be eaten.

(5) If an increase in the diet is ordered by the physician, add the prescribed number of 100 calorie portions from those listed below:—

(a) potatoes, boiled or baked—5 ounces.

(b) bread, one and a half thin (1 ounce) slices.

(c) butter, margarine or fat— $\frac{1}{2}$ ounce.

(d) bacon— $\frac{3}{4}$ ounce.

(e) jam—1 $\frac{1}{2}$ ounces.

(6) Use saccharin as sweetening agent instead of sugar.

CURRENT THERAPEUTICS

XIII—ANTIBIOTICS

BY SIR HOWARD FLOREY, M.D., PH.D., F.R.S.

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THE successful use of penicillin for the treatment of disease in man depended upon the observations that an extract from the medium on which *Penicillium notatum* had grown possessed little toxicity and that it could be present in the blood stream in concentrations sufficient to inhibit the growth of, or kill, many micro-organisms. Although the phenomenon of antibiosis, that is, the interference with the growth of one micro-organism by another, had been frequently observed from 1877 onwards (*see Florey, 1945*), and attempts had been made to utilize in medicine the chemical products concerned, penicillin was the first substance of natural origin to be shown to have systemic chemotherapeutic properties in diseases caused by bacteria (Chain, *et al.*, 1940).

The stimulus provided by this discovery was sufficient to initiate a spate of work which had as its object the isolation and examination of naturally occurring antibacterial substances other than penicillin, in the hope that some of them might prove useful in a comparable fashion. During the last few years systematic observations have been made on large numbers of micro-organisms, and practically all the named species of *Penicillia* and *Aspergilli*, as well as many *Basidiomycetes* and other fungi, have been examined for their ability to produce antibiotics. It is now known that hundreds of species of fungi produce antibiotics, some of which have been investigated in some detail. In a similar fashion large surveys of actinomycetes and bacteria have been made, and antibacterial products produced by certain flowering plants have been recognized.

It is now relatively easy to determine whether in certain defined conditions micro-organisms produce antibiotics, but their production and extraction in sufficient quantity for any further progress is often a long and arduous business. Consequently, relatively few of these substances have been extracted in a purified form. Nevertheless, at least ninety such substances are known at the present time.

It will be convenient to consider under the different groups of organisms concerned what has been the harvest, from the therapeutic point of view, of the enormous amount of work expended on the subject—work which initially involves manipulation on a very small scale, and extends to that carried out in large factories.

FUNGI

A very brief statement will suffice under this heading, for with the exception

of penicillin none of the fungal products so far extracted and examined has proved to have any therapeutic importance. It has been shown, however, that some 23 species of *Penicillia* and seven of *Aspergilli*, taken for the most part from type culture collections, produce substances which are either the same as, or very similar to, the penicillin produced by *P. notatum*.

ACTINOMYCETES

This great group of micro-organisms has proved to be a prolific source of antibiotics, many of which are too toxic to be of therapeutic importance, although some are unquestionably valuable therapeutic agents. The best known of the latter is; of course, streptomycin, which is produced by *Streptomyces griseus*. As a subsequent article is to be devoted to this drug it will suffice to mention here that it is now produced on a large scale in the United States and that it has been subjected to pharmacological, bacteriological, and chemical investigation, and is used on a large scale in the clinic.

Extensive surveys have been made of actinomycetes obtained from soil in different parts of the world, particularly by Waksman, Geiger, and Reynolds (1946) and Burkholder (1946), who examined 10,000 and 7,369 new isolates respectively. These and other surveys have shown that the elaboration of antibiotics is a widespread attribute of actinomycetes. The examination of the chemical substances produced, and their subsequent biological investigation, is proceeding. Already two substances, probably of great importance to practical medicine, have been discovered.

CHLOROMYCETIN

One of the organisms examined by Burkholder (1946) in his large survey was shown by Ehrlich *et al.* (1947) to yield a crystalline substance called chloromycetin, which contains a considerable amount of chlorine in its molecule, and which is powerfully antagonistic to a large number of bacteria.

TABLE I

CONCENTRATION OF CRYSTALLINE CHLOROMYCETIN CAUSING INHIBITION OF TEST ORGANISM

Species	µg./ml.	Inhibition per cent.
<i>Brucella abortus</i>	2.0	100
<i>Bacterium coli</i>	0.33	50
<i>friedländeri</i>	0.33	50
<i>Mycobacterium tuberculosis</i> (H37Rv)	12.5	100
<i>Proteus</i> sp.	0.33	50
<i>Salmonella schottmülleri</i>	0.33	50
<i>Shigella sonnei</i>	0.2	50
<i>Staphylococcus aureus</i>	1.0	50

The above table gives some idea of its range. The inhibition was measured turbidimetrically, with the exception of the observations on *Br. abortus* and *Myco. tuberculosis*.

Even more remarkable than its antibacterial action is its powerful action against rickettsiæ. Thus in screening tests Ehrlich *et al.* (1947) showed that it possessed some activity in the chick embryo against *R. prowazeki*, the causative organism of epidemic typhus. These results were described in detail by Smith *et al.* (1948). Smadel and Jackson (1948) showed a clear-cut therapeutic response in mice infected with *R. orientalis* treated either by parenteral injection or by mouth, and found a protective effect in a number of rickettsial infections in the chick embryo. Activity was also seen against the viruses of psittacosis and lymphogranuloma in chick embryos and mice, but not against influenza or variola viruses. The effect against viruses was about as good as that achieved with penicillin and sulphadiazine.

Chloromycetin has low toxicity for animals. For example, the LD₅₀ for mice was 245 mg./kg. administered intravenously. When given orally, 1 g./kg. produced depression and 1.25 g./kg. prostration from which recovery occurred. Gain of weight in mice was slightly retarded when the drug was administered repeatedly (100 mg./kg. daily, subcutaneously for fifteen days). Similar results were obtained in dogs and rabbits. There was no evidence of liver or kidney damage.

An important observation was that chloromycetin was absorbed not only after subcutaneous and intramuscular injection when dissolved in propylene glycol, but also from the gastro-intestinal tract.

Ley, Smadel, and Crocker (1948) investigated the fate of chloromycetin in normal men. They found that within thirty minutes after a single oral dose of 2 g. appreciable amounts of the drug could be demonstrated in the blood and urine. None was present at the end of eight hours. An initial dose of 1 g. followed every four hours by 0.2 g. was sufficient to maintain a detectable level of the substance in the blood. About 10 per cent. appeared in the urine. No toxic effects were observed.

These experimental results were followed up by clinical tests on natural rickettsial infections in man. The results have been most striking and leave no doubt that in chloromycetin a drug of first-rate importance has been discovered.

Smadel, Léon, Ley and Varela (1948) treated five patients seriously ill with epidemic typhus. Treatment was begun between the fifth and eighth days of the disease. In all cases there was a rapid fall in pulse rate and temperature, the delirium disappearing within three days and the rash within three to five days. Payne *et al.* (1948) reported in detail dramatic results in six cases of epidemic typhus and stated that ten more cases had been successfully treated. Good results were obtained by the oral administration of as little as 0.5 g. twice daily. Response to therapy was very rapid and the patients became convalescent within three days.

Smadel *et al.* (1948) reported the treatment of twenty-five cases of scrub typhus (due to *R. nipponica*). They obtained dramatic results by the administration of the drug for as short a time as twenty-four hours. Fall of temperature and improvement of symptoms were rapid, and convalescence was accelerated. Initially they administered 50 mg./kg. by mouth, and then 0.2 to 0.3 g. every two to four hours for a variable time.

No doubt other cases have now been treated and further reports may be expected.

Chloromycetin is not only active against rickettsiæ, but against such organisms as *S. typhi*, for which effective chemotherapeutic agents are at

present lacking. Reports of its use in this and other diseases will be awaited with interest.

AUREOMYCIN

At the present time only preliminary and incomplete published results on this interesting antibiotic have reached this country. A symposium to discuss it was held at the New York Academy of Sciences on July 21, 1948, but the printed account of this is not yet available. The information below is taken from the article of Bryer *et al.* (1948). The substance investigated by these authors was supplied as a yellow crystalline hydrochloride prepared from a strain of *Streptomyces aureofaciens*. It was soluble in distilled water but less so in saline, solutions being very acid (pH 4.5). In alkaline solution the antibiotic deteriorated rapidly.

This antibiotic inhibited the growth of a number of gram-positive and gram-negative organisms. Bryer *et al.* gave the following figures:—

TABLE 2

Organism	Concentration inhibiting growth µg./ml.
<i>Str. pyogenes</i> , groups, A, D, F, and G	0.3 to 1.25
<i>Str. faecalis</i> (three strains)	0.3 to 1.25
<i>Str. pneumoniae</i> , types 1, 2, and 3	0.1 to 0.3
<i>Staphylococcus</i>	0.6
<i>Bact. coli aerogenes</i>	5.0
<i>Bact. friedländeri</i>	1.0 to 5.0
<i>H. influenzae</i>	2.0
<i>Br. suis</i>	0.75
<i>Br. abortus</i>	0.75

The antibiotic appeared to be bacteriostatic rather than bactericidal, and in the presence of 50 per cent. of serum about 50 times the above concentrations were necessary to produce inhibition.

Wright, Sanders, Logan, Prigot, and Hill (1948) mentioned that in a personal communication to them Wong and Cox had stated that it was active against many rickettsiae and certain viruses, and in particular the virus of lymphogranuloma inguinale, intracerebral infection in mice being effectively treated.

The toxicity of aureomycin injected intravenously appeared to be not inconsiderable, the LD₅₀ for mice being between 50 and 100 mg./kg. of body weight. By subcutaneous injection the LD₅₀ was between 3000 and 4000 mg./kg. Dogs and rats seemed to be susceptible to about the same extent. No data were given for the toxicity following oral administration. There appeared to be a mild to severe reaction (necrosis) at the site of injection. The injections were given in 1 per cent. procaine solution, presumably because of severe pain caused by the antibiotic.

Aureomycin was detected for about 1 hour in the blood serum of rabbits and dogs following intramuscular injections of doses of 20 mg./kg. and 40 mg./kg. respectively, but none was detected in the cerebrospinal fluid. In a man weighing about 68 kg., 500 mg. given orally produced a detectable blood level. The substance was excreted in the urine, the concentration in the man following oral administration being 40 to 80 µg./ml.

Protection tests performed in mice showed that the oral administration of the drug gave some protection against *Str. pyogenes*, but not against pneumococcus type 1 or *Bact. friedländeri* type A. Better protection was secured by parenteral injection of the drug.

Attempts are being made to use aureomycin for the treatment of disease in man.

Bryer *et al.* (1948) considered that five patients suffering from Rocky Mountain spotted fever (due to *Rickettsia rickettsi*), two patients with infection of the urinary tract due to *Bact. coli.*, one patient with brucellosis, and two with typhoid fever were benefited by the oral administration of aureomycin. Wright *et al.* (1948) treated 25 cases of lymphogranuloma inguinale by the intramuscular injection once daily of 10, 20, and in one case 40 mg., dissolved in 2 ml. In the later cases isotonic sodium chloride was used as the diluent. The preliminary results recorded were such as to encourage the belief that the drug, even in this very small dosage, influenced the disease to the patients' benefit.

Braley and Sanders (1948) applied a solution containing 0.5 per cent. of aureomycin borate in isotonic salt solution at pH 7.5 to 7.8 to the eye for the treatment of a number of infective conditions. Their preliminary report stated that this solution did not irritate the eye when applied in the form of drops. There was some evidence that conjunctivitis caused by staphylococci, pneumococci, influenza bacillus and a virus (inclusion conjunctivitis) was benefited, and it was possibly of value in other conditions. The authors considered that aureomycin was "a valuable addition to our armamentarium of antibiotics".

Thus, the little that has so far been published makes it appear that aureomycin has clinical possibilities, although clearly much more information will be necessary before its real value in medicine can be assessed. The facts that it is partially inactivated by serum *in vitro*, and that stable solutions are very acid, would both appear adverse to its usefulness in the treatment of disease.

The outstandingly interesting property of chloromycetin and aureomycin is, of course, their activity under experimental conditions against many species of *Rickettsia* and some viruses. The clinical results achieved with chloromycetin leave no possible doubt that it is a drug of first-rate importance for the chemotherapeutic treatment of a number of serious diseases hitherto outside the range of chemotherapeutic attack. These results also show that a chemotherapeutic agent can attack micro-organisms that are intracellular, which raises hopes that diseases caused by viruses may not be beyond chemotherapeutic reach.

BACTERIA

Many species of bacteria have been shown to produce antibiotics, and indeed it was a substance from *Pseudomonas pyocyanea* which was the first antibacterial product derived from a micro-organism to receive extensive investigation in the clinic. Since then many bacterial antibiotics have become known, and some have been produced in a highly purified form, but the substances that have reached the stage of clinical investigation have all been derived from the group of the aerobic spore-forming bacilli.

The first of these to be investigated was *tyrothricin*—a mixture of gramicidin and tyrocidine (Dubos, 1939). It was found to be much too toxic for the treatment of disease by parenteral injection. It has, however, had extensive clinical trial as a local application to such lesions as ulcers infected with streptococci and other gram-positive organisms susceptible to it. Although of considerable value as a local application it has been little used in this country, but it is still on sale in the United States.

More recently, antibiotics produced by the aerobic spore-forming bacilli have been extensively examined, and two products have reached the stage of clinical trial. These antibiotics appear to be polypeptides of different constitutions. Some act principally against gram-positive organisms. Included in these are: *bacitracin* (Jern and Meleney, 1945; Johnson, Anker, and Meleney, 1945; Eagle *et al.*, 1947; Goorley, 1947; Hoff, Bennett, and Stanley, 1947; Johnson *et al.*, 1947; Meleney and Johnson, 1947; Scudi and Antopol, 1947; Scudi, Clift, and Krueger, 1947; Anker *et al.*, 1948); *subtilin* (Jansen and Hirschmann, 1944; Salle and Jann, 1945, 1946, a, b, c, d and e; Salle, 1947; Anderson *et al.*, 1946; Chin, 1947, 1948; Feeney; Lightbody, and Garibaldi, 1947; Goodman and Henry, 1947; Dimick *et al.*, 1947, Lewis, *et al.*, 1947; Stubbs *et al.*, 1947; Wong, Hambly and Anderson, 1947; Magarão, Arriagada, and Thales, 1944; Richou, 1945; Ramon and Richou, 1945, 1947, a, b, and c; Remlinger and Bailly, 1946); *licheniformin* (Callow and Hart, 1946; Scudi, Boxer, and Jelinek, 1946; Hart and Hills, 1947; Callow, Glover, and Hart, 1947; Callow, Glover, Hart, and Hills, 1947). All these inhibit the growth of organisms in a range somewhat similar to that of penicillin, that is to say, with their greatest activity against gram-positive organisms. The two last substances are particularly interesting because they inhibit the growth of the tubercle bacillus *in vitro*. Others produced by *B. polymyxa* (the polymyxins) act principally against gram-negative organisms.

All the antibiotics mentioned have been found to produce a systemic chemotherapeutic effect when used against experimental infections with susceptible organisms in animals, but only some members of one group, the polymyxins, have been so used in man, although bacitracin has been used with success for the local treatment of infections.

Polymyxins.—In England, Ainsworth, Brown, and Brownlee (1947) briefly described the preparation and properties of a substance, aerosporin, produced by *B. aerosporus*. Later, Brownlee and Bushby (1948) described these observations in more detail. At about the same time Stansly, Shepherd, and White (1947) in the United States described the production of an antibiotic, polymyxin, by *B. polymyxa*. The British and American workers have already contributed much to the understanding of the polymyxins, of which there are at least four closely related types called polymyxin A, B, C and D. They all appear to be basic polypeptides, together with a fatty acid component, the molecular weights varying from about 1000 to 1300. They appear to have approximately the same antibacterial range. Table 3 gives the range for polymyxin A and makes a comparison with the activity of streptomycin. Its action was shown to be bactericidal, and so far it has not been possible to induce resistance of organisms to polymyxin in fluid cultures.

The polymyxins are absorbed after intramuscular and subcutaneous

injection but not after oral administration. Although they are apparently excreted but little in the urine, they have been found to cause damage to the kidneys of animals and albuminuria in man. It is stated, however, that polymyxin B, obtained from a British strain of *B. polymyxa*, does not damage the kidneys.

TABLE 3
ANTIBACTERIAL ACTIVITY OF POLYMYXIN A

Organism	Smallest concentration inhibiting growth in $\mu\text{g./ml.}$	
	polymyxin	streptomycin
<i>Haemophilus bronchisepticus</i>	0.08	>16.0
" <i>influenzae</i>	0.02	1.0
" <i>pertussis</i>	0.04	0.5
<i>Bacterium aerogenes</i>	0.2	12.5
" <i>coli</i> (non-veterinary)	<0.04—0.08	16.0
<i>Salmonella choleraesuis</i>	0.16	31.25
" <i>enteritidis</i>	0.64	8.0
" <i>paratyphi</i> A	<0.04	16.0
" " B	0.08	8.0
" <i>typhi</i> (Rawlings)	0.08	16.0
" <i>typhimurium</i>	0.64	125
" (five species)	0.16—0.64	62.5—125
<i>Shigella flexneri</i>	0.16	8.0
" <i>shigae</i>	0.08	4.0
" <i>sonnei</i>	0.16	4.0
<i>Neisseria catarrhalis</i>	0.08	1.0
<i>Vibrio cholerae</i>	0.32	8.0
<i>Pasteurella bovisseptica</i>	0.4	12.5
" <i>pestis</i>	0.4	12.5
<i>Pseudomonas pyocyanea</i>	0.64	4.0
<i>Brucella abortus</i>	1.6	1.6

The LD₅₀ of polymyxin A injected intravenously is 6.14 mg./kg., which means that it is a relatively toxic substance. No data for polymyxin B are available. However, these substances are so active against bacteria that there is a range of dosage within which they can safely act in the animal body as systemic chemotherapeutic agents. Polymyxin A has been shown to be effective in mice against experimental infections with *H. pertussis*, *Bact. coli*, and *S. typhi*. Data on polymyxin B are not yet available.

A few clinical trials have been carried out, mainly so far with polymyxin A, and beneficial results have been claimed in whooping-cough and gastro-enteritis in children (treated orally). In certain genito-urinary infections with organisms sensitive to polymyxin B, good results have been claimed with that drug. Clearly the polymyxins are interesting antibiotics with possible uses in the clinic, but much more work is required before judgment of their ultimate usefulness can be made, and much depends upon whether polymyxin B in therapeutic doses can be shown not to damage the kidneys of man.

A conference on the polymyxins was held at the New York Academy of Science on May 21-22, 1948, but the publications are not yet available. The published papers are Greer (1928), Ainsworth, Brown, and Brownlee

(1947), Stansly and Schlosser (1947 a and b), Stansly, Shepherd, and White (1947), Brownlee and Bushby (1948), and Swift (1948). Information has also been obtained from a brochure prepared by Messrs. Burroughs Wellcome & Co. (U.S.A.) Inc.

Bacitracin, licheniformin, subtilin.—These polypeptides, acting principally against gram-positive organisms, have been shown to be effective as systemic chemotherapeutic agents in experimental infections in animals. Bacitracin and licheniformin—both of which are probably mixtures—unfortunately damage the kidney. So far no therapeutic trials of the drugs administered parenterally to man have been recorded. Few pharmacological data are available about subtilin, which has also not apparently been used in man. Bacitracin has been investigated extensively and has been used successfully by local application to treat lesions in man due to susceptible organisms (Meleney and Johnson, 1947).

CONCLUSION

This short review will suffice to show that only a few of the large number of antibiotics investigated in the laboratory reach the stage of clinical trial, and of these not all may prove to be suitable for general medical use. Nevertheless, the harvest is rich, for in chloromycetin and possibly in aureomycin we have drugs of great power against a whole range of organisms previously quite untouched by chemotherapy. Whether the products of the spore-forming bacilli will find a permanent place in medicine only further investigation will show. These advances in therapeutics tend to emphasize the importance of detailed bacteriological knowledge for the rational and successful treatment of infectious disease. The new agents, remarkable as they are, will only yield satisfactory results when their administration is guided by a sound knowledge of their properties. Unfortunately the manufacture of antibiotics is slow and difficult, demanding great material resources, so that the substances here discussed are not likely to be widely available in the near future unless successful synthetic processes for making them are soon developed.

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REVISION CORNER

HOARSENESS

"It sounds like a horse," Alice thought to herself. And an extremely small voice, close to her ear, said, "You might make a joke on that—something about 'horse' and 'hoarse' you know."

THIS quotation from Lewis Carroll illustrates the popular attitude to the symptom of hoarseness, which is often regarded as a joke. This is probably owing to the relative frequency of attacks of *simple acute catarrhal laryngitis*, usually unassociated with much malaise. Most of us can remember a number of such attacks, which in adult life make one feel slightly ludicrous, and in childhood give a sense of importance; the latter perhaps partly explaining the occurrence of aphonia as an hysterical symptom. Further, *chronic laryngitis* is a common benign condition, which, although traditionally associated with clergymen, in these days of shorter sermons is more frequently met with in such jovial folk as the professional comedian or racing tipster. The importance of this attitude is that both the patient and his doctor may discount the first warning of more serious disease. No doubt many doctors have by now read Scott Stevenson's absorbing book "Morell Mackenzie" describing the early days of laryngoscopy and the illness of the Crown Prince Frederick of Germany, "who when 55 years old began to show evidence of slight but persistent hoarseness".

FUNCTIONAL FACTORS

Hoarseness is a symptom that is of interest to the general practitioner, as it overlaps a number of specialties. First must be considered whether it is emotional or organic in origin, or alternatively whether there is an emotional exaggeration of an underlying disease. The latter association may present some difficulty, as for instance when a functional aphonia is superimposed on an organic dysphasia. *Hysterical dysphonia* is usually fairly obvious:—

A girl of twenty-six, who four days previously had awakened with loss of voice and was only able to speak in a whisper, phonated normally on coughing. Ten weeks before, she had been greatly upset by the sudden death from cerebral hæmorrhage of her friend aged thirty-five, to whom she was talking at the time. In 1941, after a bomb incident, she had lost her voice for three days. She had also had trouble over her work. Her dysphonia responded to speech therapy and psychotherapy, but she developed other hysterical symptoms.

In any such case, however, in which there is doubt, laryngoscopy will show normal cords moving normally with respiration.

ORGANIC FACTORS

Organic diseases may be subdivided into those local disorders which affect the vocal cords or larynx, those which cause paresis of one or both cords, and those general conditions which affect the voice indirectly.

Neoplasms.—The first stage in the investigation of a case of persistent hoarseness is laryngoscopy. It is very desirable that this should be done by an experienced laryngologist. This examination should exclude growths such as papilloma, fibroma, or carcinoma, although occasionally direct laryngoscopy may also be required. In considering the history, it should be remembered that vocal abuse causing chronic laryngitis has been held to be a factor in the etiology of quite a number of cases of cancer of the larynx. There may also be the additional feature of perichondritis, which is especially met with after deep X-ray or radium treatment. An external tumour, such as a colloid goitre, may press on the larynx or trachea.

Syphilitic laryngitis is perhaps less common than formerly, but a blood Wassermann

reaction may reasonably be regarded as a routine investigation, as it may also be relevant in cases with central nervous disease or thoracic aneurysm.

Hoarseness as a symptom of *pulmonary tuberculosis* is still too often forgotten.

A man of fifty-six had a four months' history of intermittent hoarseness following a series of colds, associated with fatigability and occasional coughing and night sweats. For seven weeks his hoarseness had been persistent and his doctor had treated him with gargles. He had marked physical signs at both apices, and chest X-ray showed active bilateral tuberculosis.

Laryngeal diphtheria in children is often difficult to diagnose, and occasionally postdiphtheritic neuritis occurs in a case in which the acute illness has been missed. This may cause laryngeal paresis, although disturbance of vision, palatal palsy and peripheral neuritis are more common.

LARYNGEAL PALSY

Considering next the causes of laryngeal palsy, involvement of the recurrent laryngeal nerve in the neck itself is apt to be overlooked.

A man of sixty-seven, with a three months' history of hoarseness, was referred to me for paresis of the left vocal cord. I found nothing abnormal on full general and neurological examination or chest X-ray, and the blood Wassermann proved negative. It was not until a year later that an inoperable carcinoma of the thyroid gland with involvement of the lymph nodes became obvious, the patient dying four months after the diagnosis was made, despite deep X-ray treatment.

Three years after this experience another man, with paralysis of the left vocal cord, aged forty-seven, in whom bronchoscopy, œsophagoscopy, chest X-ray and blood Wassermann had all proved normal, was referred to me. On palpating the thyroid I found a small, stony-hard nodule about 3 x 2 cm. in the left lobe of the thyroid, fixed to the trachea.

These cases illustrate the point that *carcinoma of the thyroid* may start at the back of the gland and so involve the nerve early at a time when the growth may easily be overlooked. Damage to the nerve during thyroidectomy is evident after the operation.

Within the chest *primary and secondary growths, Hodgkin's disease, aortic aneurysm* and occasionally the enlarged left auricle in *mitral stenosis* may all press on the recurrent laryngeal nerve. Such conditions are usually evident on examination or chest X-ray, although secondary deposits in the axillary glands may be missed.

LESIONS OF THE CENTRAL NERVOUS SYSTEM

In the central nervous system itself, supranuclear lesions may be discounted, as only very rarely, if bilateral, may they involve the movements of the vocal cords. Nuclear lesions are more important: thus hoarseness may be the presenting symptom in some cases of *posterior inferior cerebellar artery thrombosis*, which will have a sudden onset and also show the characteristic crossed anaesthesia and ataxia. In *syringo-bulbia* it is not usually one of the early symptoms. In the bulbar palsy of *motor neurone disease* a characteristic dysarthria is often the presenting symptom, but not hoarseness as such. *Bulbar poliomyelitis* may rarely cause difficulty, especially if the acute attack is missed, as in a case arising after tonsillectomy during an epidemic. Bilateral abductor paralysis of the vocal cords may occur in *tuberculosis*, and I recollect such a patient, who had normal pupil reactions, although absent tendon jerks and loss of deep sensibility. The vagus may also be involved in the posterior fossa of the skull, by tumours, syphilis, and periostitis arising from middle-ear infections.

OTHER CONDITIONS CAUSING HOARSENESS

Among general conditions, *myasthenia gravis* may cause hoarseness, although slurring of speech is more common, and fatigability is the characteristic feature. *Acromegaly* causes a deepening of the voice owing to the enlargement of the larynx, rather than a true hoarseness.

In conclusion I would refer to a patient, whose hoarse voice on the telephone was obvious when he rang up for an appointment. He was a man of fifty-three, who had attended at a throat hospital ten months before for this symptom, and had also attended six other special hospitals or specialists for various symptoms. His appearance suggested *myxœdema*, and on investigation his basal metabolic rate proved to be minus 31 per cent. The laryngologist reported some œdema of the false cords and arytenoids in keeping with the sub-thyroid state. The electrocardiograph was also characteristic, and there were some signs of heart failure. After two months' treatment with thyroid, 3 grains (0.2 g.) daily, his voice had recovered, and his electrocardiograph and general condition had returned to normal.

This case illustrates the need for the general medical approach referred to at the beginning of this article.

N. G. HULBERT, M.D., M.R.C.P.

THE DIFFERENTIAL DIAGNOSIS OF GLYCOSURIA

GLYCOSURIA means by common usage that reduction is shown when urine is examined by a simple chemical test. The only reducing substance of pathological significance is the glucose of diabetes mellitus with its inevitable hyperglycæmia. The highest limit of capillary blood sugar in the normal person does not exceed 200 mg. per 100 ml.

CLASSIFICATION

(1) *Glycosuria without hyperglycæmia*

(a) Glycosuria due to a low renal threshold for glucose. This is true renal or orthoglycæmic glycosuria, sometimes incorrectly called renal diabetes or diabetes innocens.

(b) Glycosuria due to reducing substances other than glucose, such as lactose, pentose and lævulose.

(2) *Hyperglycæmic glycosuria*

Diabetic glycosuria
 / With definite symptoms.
 \ Symptomless.

Non-diabetic hyperglycæmic glycosuria:—

Oxyhyperglycæmia, the so-called lag storage of glucose.

Thyrotoxicosis and other endocrine disorders.

Liver disease.

Previous long-standing carbohydrate restriction.

Cerebral bleeding and head injury.

Toxic and septic states.

URINE TESTS

False reports of glycosuria in fit people are so common that a prudent first step in such cases is a reliable test of urine passed one hour after a starchy meal.

A clean test tube is filled almost to the brim with urine and emptied by inverting the tube for a moment. One inch of Benedict's qualitative solution is added to the wetted tube which is then placed in boiling water for five minutes. No reduction means no glycosuria, but even the green precipitate of slight reduction demands further investigation.

In some diabetics, symptoms of thirst, polyuria, wasting or ketosis are so definite that glycosuria merely confirms the diagnosis, and treatment need not wait on blood sugar estimation. Urine from cases of any severity shows a positive nitroprusside test, but traces of ketones are sometimes present in the urine of children or fasting patients who are not diabetic.

Rothera's test.—Materials: Rothera's crystals, made by mixing sodium nitroprusside, 1 part, with ammonium sulphate, 80 parts; strong solution of ammonia. Mix in a test tube, $\frac{1}{2}$ an inch of Rothera's crystals, $\frac{1}{2}$ test tube of urine, and $\frac{1}{2}$ an inch of

ammonia. After five minutes, shake again and observe the colour, which in the presence of ketone bodies varies from the pale lilac of a dilute solution of potassium permanganate to a purple so deep that light is not transmitted.

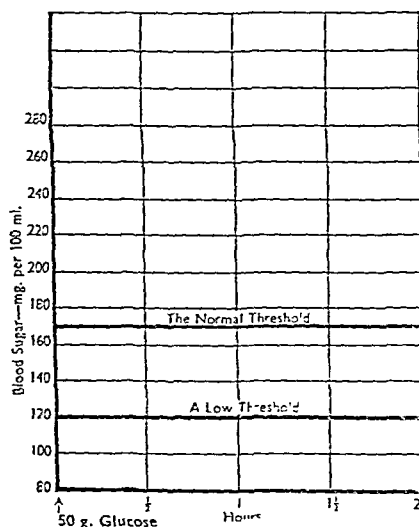
Diabetic glycosuria without symptoms is by no means rare. On the other hand, glycosuria from any cause may be associated with such misleading symptoms as the dry mouth of the patient with oral sepsis; the minor thirst, frequency and pruritus of normal pregnancy; the urinary symptoms of prostatism, or the coma of cerebral bleeding.

BLOOD SUGAR ESTIMATION

Blood sugar estimation is essential for all cases without definite symptoms of diabetes mellitus. Fasting levels are generally of less value than estimations which are considered in relation to the time of the previous meal, with a rough assessment of its carbohydrate content. The normal lowest level, at two to four hours after food, lies between 70 and 120 mg. of glucose per 100 ml., and the peak is reached in a half to one and a half hours after feeding. Often enough the one test will prove or exclude diabetes mellitus but few insurance offices accept the disproof of diabetes afforded by a single blood sugar estimation; so for these and all cases in which any doubt remains the next step is a *glucose tolerance test*.

For at least two weeks before the test the patient should take a full diet, but immediately beforehand he should fast for six to eight hours. Samples of blood and urine are collected in the fasting state and the patient swallows 50 g. of glucose in 100 ml. of water. Thereafter urine and blood are taken at intervals of half an hour for two hours. The urine is tested for sugar as described. For the blood sugar estimations, capillary blood from the ear is examined by such convenient methods as the colorimetric analysis of Folin and Wu, or the Hagedorn and Jensen titration.

If the curve is normal the precise identification of the reducing substance is of



small importance. Lactosuria is sometimes seen in lactating women at times of breast engorgement and forced weaning. In pregnancy, non-diabetic glycosuria is due to glucose passed into the urine by the kidney at a blood concentration below the average renal threshold for glucose—170 to 180 mg. per 100 ml. The curve may give a diagnosis, or its interpretation may be so difficult that all that can be done is to reassure the patient, continue full diet and repeat the test in some months. Liver disease, hyperthyroidism, obesity and toxæmia may all give abnormal pseudo-diabetic types of curve which become normal as the patient recovers.

At this point the reader is asked to plot the curves from the illustrative cases on to the blank form. Lawrence (1947) gives the gist of the whole matter in his summary: "If the fasting

blood sugar is below 120 mg. per 100 c.c. and has returned to this figure at two hours after 50 g. of glucose, we can classify the case with confidence as non-diabetic whatever the intervening concentration of glycaemia and the accompanying glycosuria".

In conclusion I would refer to a patient, whose hoarse voice on the telephone was obvious when he rang up for an appointment. He was a man of fifty-three, who had attended at a throat hospital ten months before for this symptom, and had also attended six other special hospitals or specialists for various symptoms. His appearance suggested *myxœdema*, and on investigation his basal metabolic rate proved to be minus 31 per cent. The laryngologist reported some œdema of the false cords and arytenoids in keeping with the sub-thyroid state. The electrocardiograph was also characteristic, and there were some signs of heart failure. After two months' treatment with thyroid, 3 grains (0.2 g.) daily, his voice had recovered, and his electrocardiograph and general condition had returned to normal.

This case illustrates the need for the general medical approach referred to at the beginning of this article.

N. G. HULBERT, M.D., M.R.C.P.

THE DIFFERENTIAL DIAGNOSIS OF GLYCOSURIA

GLYCOSURIA means by common usage that reduction is shown when urine is examined by a simple chemical test. The only reducing substance of pathological significance is the glucose of diabetes mellitus with its inevitable hyperglycæmia. The highest limit of capillary blood sugar in the normal person does not exceed 200 mg. per 100 ml.

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Diabetic glycosuria / With definite symptoms.

Diabetic glycosuria \ Symptomless.

Non-diabetic hyperglycæmic glycosuria.—

Oxhyperglycæmia, the so-called lag storage of glucose.

Thyrototoxicosis and other endocrine disorders.

Liver disease.

Previous long-standing carbohydrate restriction

Cerebral bleeding and head injury.

Toxic and septic states.

URINE TESTS

False reports of glycosuria in fit people are so common that a prudent first step in such cases is a reliable test of urine passed one hour after a starchy meal

A clean test tube is filled almost to the brim with urine and emptied by inverting the tube for a moment. One inch of Benedict's qualitative solution is added to the wetted tube which is then placed in boiling water for five minutes. No reduction means no glycosuria, but even the green precipitate of slight reduction demands further investigation

In some diabetics, symptoms of thirst, polyuria, wasting or ketosis are so definite that glycosuria merely confirms the diagnosis, and treatment need not wait on blood sugar estimation. Urine from cases of any severity shows a positive nitroprusside test, but traces of ketones are sometimes present in the urine of children or fasting patients who are not diabetic.

Rothera's test—Materials: Rothera's crystals, made by mixing sodium nitroprusside, 1 part, with ammonium sulphate, 80 parts, strong solution of ammonia
Mix in a test tube, $\frac{1}{2}$ an inch of Rothera's crystals, $\frac{1}{2}$ test tube of urine, and $\frac{1}{2}$ an inch of

ammonia. After five minutes, shake again and observe the colour, which in the presence of ketone bodies varies from the pale lilac of a dilute solution of potassium permanganate to a purple so deep that light is not transmitted.

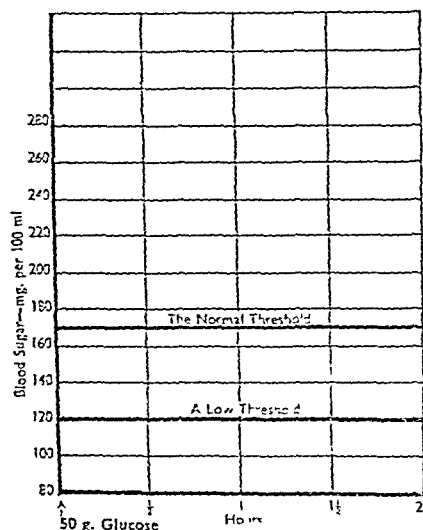
Diabetic glycosuria without symptoms is by no means rare. On the other hand, glycosuria from any cause may be associated with such misleading symptoms as the dry mouth of the patient with oral sepsis; the minor thirst, frequency and pruritus of normal pregnancy; the urinary symptoms of prostatism, or the coma of cerebral bleeding.

BLOOD SUGAR ESTIMATION

Blood sugar estimation is essential for all cases without definite symptoms of diabetes mellitus. Fasting levels are generally of less value than estimations which are considered in relation to the time of the previous meal, with a rough assessment of its carbohydrate content. The normal lowest level, at two to four hours after food, lies between 70 and 120 mg. of glucose per 100 ml., and the peak is reached in a half to one and a half hours after feeding. Often enough the one test will prove or exclude diabetes mellitus but few insurance offices accept the disproof of diabetes afforded by a single blood sugar estimation; so for these and all cases in which any doubt remains the next step is a *glucose tolerance test*.

For at least two weeks before the test the patient should take a full diet, but immediately beforehand he should fast for six to eight hours. Samples of blood and urine are collected in the fasting state and the patient swallows 50 g. of glucose in 100 ml. of water. Thereafter urine and blood are taken at intervals of half an hour for two hours. The urine is tested for sugar as described. For the blood sugar estimations, capillary blood from the ear is examined by such convenient methods as the colorimetric analysis of Folin and Wu, or the Hagedorn and Jensen titration.

If the curve is normal the precise identification of the reducing substance is of



small importance. Lactosuria is sometimes seen in lactating women at times of breast engorgement and forced weaning. In pregnancy, non-diabetic glycosuria is due to glucose passed into the urine by the kidney at a blood concentration below the average renal threshold for glucose—170 to 180 mg. per 100 ml. The curve may give a diagnosis, or its interpretation may be so difficult that all that can be done is to reassure the patient, continue full diet and repeat the test in some months. Liver disease, hyperthyroidism, obesity and toxæmia may all give abnormal pseudo-diabetic types of curve which become normal as the patient recovers.

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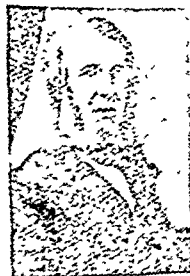
Phenobarbitone, $\frac{1}{2}$ a grain (32 mg.) b.d., and rest for a day or two is the best treatment to adopt. It is most important to calm the patient's fears and to explain that the attack is not a serious one, although the symptoms are so startling. Should further attacks occur a regimen of restriction of the fluid intake and a salt-free diet may be tried. Some cases with repeated attacks respond to treatment with nicotinic acid, 50 mg. t.d.s.

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James Stocker

interference when the bedclothes are pulled down, and will draw them back again. In particular the sign is applied to the differentiation of meningitis from typhoid fever. This is of meningitis from typhoid fever. This is probably a restriction of Stocker's original intention, and in Wilks and Bettany's "History of Guy's Hospital" the following comment is made: "His remarks, however, were always good, and many of them were long remembered; for example, if a young person was brought to the Hospital with symptoms doubtfully suggestive either of cerebral disease or fever, he would say that if on attempting to

raise his shirt to look for an eruption the patient assisted you, it was a case of fever; if he resisted, it was one of head disease—meaning, of course, that in one case the patient was simply lethargic and acted in an automaton-like manner, in the other he was irritable and full of pain."

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REPLY.—The method provisionally recommended (Knutson, J. W., *J. dent. Res.*, 1948, 27, 340) is: The child's teeth are cleaned with pumice powder in a rubber cup (5 minutes), isolated with cotton rolls and dried with compressed air. The 2 per cent. aqueous solution of sodium fluoride is applied to the teeth on a small pledget of cotton-wool and allowed to dry (3 minutes). The procedure is repeated at weekly intervals until four applications have been made, but the preliminary cleaning can be omitted after the first time. The treatment is given at the ages of three, seven, ten and thirteen years, as successive groups of teeth erupt. The solution is poisonous and precautions should be taken to prevent its unauthorized or accidental use. A useful discussion of the subject will be found in the article quoted.

PROFESSOR M. A. RUSHTON, M.D., F.D.S.

Muscular Dystrophy

QUERY (from India).—My daughter, aged twelve years, has been suffering from progressive muscular dystrophy for the past two and a half years. During this period I have given her 32 injections of prostigmin (Roche) and gynergin (Sandoz) mixed together, some 20 or 40 injections of pyridoxin (vitamin B₆), vitamin B complex and vitamin B₁₂, and orally vitamin E and glycine (B.D.H.). There has been no improvement, and her condition is deteriorating gradually. At present she is completely bed-ridden and cannot move her legs. She can only move her head. I shall be obliged if you can suggest some treatment for this child of mine.

REPLY.—The cause of muscular dystrophy is not definitely known, so there is no specific treatment. It is now thought that in normal people vitamin E is combined—during its intestinal absorption—with some other "factor"

The following table shows illustrative curves. Rothera's test negative in all specimens.

Time	(1) <i>Renal glycosuria</i>		(2) <i>Diabetic glycosuria</i>		(3) <i>Oxyhyperglycæmic glycosuria</i>	
	Benedict	B.S.	Benedict	B.S.	Benedict	B.S.
Fasting ..	0	75	0	150	0	100
50 g. glucose ½ hour ..	+	150	+++	250	++	280
1 " ..	++	130	++	240	+	200
1½ " ..	+	100	++	220	+	120
2 " ..	0	80	+	200	0	100

Curve 1 is the normal blood sugar curve, starting low—no higher than 120 mg. per 100 ml.—not rising high, and returning to a low level at two hours. The curve establishes the orthoglycæmic nature of the glycosuria and the renal threshold lies between 100 and 130 mg. glucose per 100 ml.

Curve 2 is a typical diabetic curve, starting high—higher than 120 mg. per 100 ml.—rising high and staying high at the end of two hours.

Curve 3 shows oxyhyperglycæmia, the name suggested by Lawrence (1936) for what is often called the lag-storage curve. He considers that its occurrence is due to rapid intestinal absorption and not to any defect of carbohydrate metabolism. Glycosuria in this condition occurs after meals and is absent in the latter part of the test if the threshold is normal.

References

- Lawrence, R. D. (1936): *Brit. med. J.*, **i**, 526.
— (1947): *Med. Clin. N.A.*, **31**, 289.

HERMON WHITTAKER, M.R.C.P.

NOTES AND QUERIES

Vertigo

QUERY.—During the last two or three years I have been struck by the number of people who have complained of vertigo of sudden onset, generally on rising in the morning, sometimes accompanied by sickness and nearly always requiring three to four days' rest in bed, when it passes off. No cause could be found in any of my cases. Eventually I had an attack myself and had to spend two days in bed. A colleague, whom I called in, could not explain it. I am interested in its etiology and would appreciate your comments as to whether others have reported similar experience.

REPLY.—A momentary feeling of dizziness is not uncommonly experienced by those whose blood pressure is rather low, when they rise suddenly from the recumbent position to the upright. However, this is not true vertigo, there being as a rule no sensation of turning, either of things seen or of the patient himself. The attacks of vertigo described, particularly those associated with sickness, are almost certainly those of Ménière's disease. These often occur on rising in the morning. As a rule there is some associated deafness and tinnitus, but

this is not necessarily the case. The attacks of vertigo tend to occur in bouts and there may be an interval of many months or even a number of years between the bouts. Many patients will recall a single isolated attack of vertigo years before further attacks have supervened.

An examination of the central nervous system should be made to exclude such causal factors as eighth nerve tumour, disseminated sclerosis, and other diseases of the nervous system. With chronic suppurative otitis media, particularly with cholesteatoma, attacks of vertigo are sometimes complained of, and this indicates that the disease is spreading towards the labyrinth, and in some cases it will be found at operation that the bony wall of the external semicircular canal has been eroded. Eustachian obstruction, rather surprisingly, rarely causes vertigo and this symptom practically never occurs with acute otitis media. It is sometimes seen in cases of acute maxillary sinusitis. With sudden complete loss of hearing from a traumatic or a toxic cause (e.g. influenza or mumps) the striking symptoms of the destruction of the labyrinthine function are at first, in most cases, the giddiness and the vomiting. In cases of Ménière's disease there is as a rule tinnitus but this may be neg-

gible, and at first the deafness may be very slight and may be overlooked. The deafness is nerve deafness in type, with the loss of hearing most marked for the highest tones. It is likely in the cases described that the attacks are the first of Ménière's disease and it is to be expected that sooner or later, but perhaps not for some years, further attacks of giddiness will be experienced.

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REPLY.—The cause of muscular dystrophy is not definitely known, so there is no specific treatment. It is now thought that in normal people vitamin E is combined—during its intestinal absorption—with some other "factor"

to form a complex which is necessary for the metabolism of muscle. Failure to form this complex is believed to be the cause of muscular dystrophy. Repeated efforts have been made to synthesize this missing complex, both chemically and by the action on vitamin E of gastrointestinal preparations. Until such a synthesis is achieved patients should be given ample physiological amounts of *natural* vitamin E in all its forms, together with physiological amounts of the other vitamins. This is best achieved by giving one ounce (28.4 g.) daily of a reliable commercial preparation of dried wheat germ, together with plenty of fresh green vegetables, fresh dairy produce and fresh meat. Rancid foods and fats must be avoided as rancidity destroys vitamin E. Single synthetic vitamins should be avoided and no drugs, hormones, faradic stimulation or other measures are of any value. Septic foci must be treated: surgical treatment of contractures is generally valueless and may be injurious. Even mild bronchitis is a serious emergency which must be treated immediately, both with sulphonamides and penicillin, since these patients, often

being too weak to cough, may rapidly develop a fatal broncho-pneumonia.

FRANKLIN BICKNELL, D.M., M.R.C.P.

Nocturnal Hyperæsthesia

QUERY.—What is the significance of the symptom in a middle-aged woman of waking in the night with a pain like pins and needles in the fingers, apparently not caused by lying in an awkward position?

REPLY.—This is not a characteristic symptom of any known disease. Assuming that the pins and needles occur in both hands and all fingers, there are not many possibilities: (1) Mechanical reasons, such as spinal arthritis, or cervical cord tumour. (2) Diabetes mellitus: the symptoms usually come on immediately on going to bed and do not wake the patient. (3) Peripheral neuritis or subacute combined degeneration of the cord associated with pernicious anemia. Scalenus anticus syndrome or cervical ribs are very unlikely. In the complete absence of any abnormal physical signs, the symptoms are probably of no serious significance.

H. K. GOADBY, M.D., F.R.C.P.

PRACTICAL NOTES

Intravenous Oxygen in Bronchial Asthma

DETAILS are given by H. Markow and his colleagues (*Annals of Internal Medicine*, October 1948, 29, 607) of the results obtained with intravenous oxygen in eight patients with severe bronchial asthma. "One hundred per cent. (commercial) oxygen" was given intravenously at a rate of 600 ml. per hour, and at a pressure "just sufficient to clear the glass viewing tube, proximal to the intravenous needle, of the blood that has influxed into it upon venipuncture, i.e., just above venous pressure". The oxygen was allowed to flow without interruption for periods of 2 to 17 hours, and the total volume of oxygen administered ranged from 3000 to 22,000 ml. The most striking response to this form of therapy was a rise in the vital capacity, ranging from 300 ml. (30 per cent.) to 1300 ml. (87 per cent.). This increase in vital capacity was maintained for a considerable time in some patients: in five it was maintained for a month, whilst in one it was not until eight months later that it fell below pre-treatment level. Clinically, the important finding was that in every case there was early relief of symptoms, appearing within five minutes to two hours. The duration of clinical improvement varied with the amount of oxygen given: in two patients who received 3000 and 4000 ml. respectively, there was

recurrence of symptoms within ten days, whereas in the five patients receiving 8000 to 22,000 ml. clinical improvement was maintained for four to six months. As clinical improvement often extended beyond the period of increased vital capacity, it is pointed out that this increased vital capacity is unlikely to be the entire explanation of the relief of asthmatic attacks. With regard to the prejudice against giving oxygen intravenously, it is stated that "there is no danger of air embolism or vapour block if the intravenous administration of oxygen is carefully regulated and kept within physiologic volume, pressure and flow-rate".

The Diagnostic Value of Inguinal Adenitis in Primary Syphilis

In view of the differences of opinion as to how early inguinal adenitis develops in primary syphilis, W. Fowler (*British Journal of Dermatology and Syphilis*, September 1948, 60, 279) has re-investigated the problem in 116 males with syphilitic chancres of the genitals. The results may be summarized as follows:—Of 18 patients seen within one to three days of the appearance of the chancre, 73 per cent. had adenitis when first seen. Of 41 seen within four to six days of the appearance of the chancre, 78 per cent. had adenitis. The comparable percentages for the 32 seen within seven to

fourteen days, and the 25 seen within fifteen or twenty-one days, were 84 and 100 respectively. In other words, "enlargement of the inguinal glands occurs soon after the chancre appears and in a sufficient number of cases to warrant its being regarded as an important sign in the diagnosis of the chancre". Another interesting and important observation was that in 15 cases there was contralateral adenitis alone, whilst in three other cases the inguinal glands on the opposite side to the chancre were larger than those on the same side. As a control, 52 cases of "non-specific infective lesions with adenitis" were investigated, and in none of these was there enlargement of the inguinal glands on the opposite side. It is therefore suggested that "the combination of an infective lesion of the male genitals with enlargement of the glands in the opposite inguinal region alone is strong presumptive evidence of syphilis".

Treatment of Otitis Externa

FOR the treatment of both acute and chronic otitis externa, J. S. Walker (*Bulletin of the Johns Hopkins Hospital*, September 1948, 83, 225) recommends iso-par. Iso-par is a mixture of water-insoluble isoparaffinic acids partially neutralized with iso-octyl hydroxybenzyl-dialiphatic amines. For the purpose of this investigation it was used as an ointment containing 17 per cent. of iso-par and 4 per cent. of titanium dioxide in an ointment base consisting of beeswax, cetyl alcohol, lanolin and petroleum. The course of treatment followed was to cleanse the auditory canal with alcohol-soaked applicators, and then apply a thin coating of the iso-par ointment. This procedure was repeated as often as necessary. In patients subject to recurrent attacks of otitis externa the ointment was applied weekly as a prophylactic measure. Of 41 patients in whom the effect of iso-par was studied, 25 (60 per cent.) were cured, 10 (24 per cent.) were improved, and six (16 per cent.) were unaffected. The duration of treatment varied considerably—from two months to five days. No sensitization to iso-par was noted, and it was found to be most effective in relieving local pain and pruritus.

Small Ophthalmic Bandages

COMMENTING on the fact that small ophthalmic bandages are little known and still less used, L. Gát (*American Journal of Ophthalmology*, October 1948, 31, 1306) describes two types which are in general use at the University Eye Clinic, Debrecen, Hungary. The most simple of the two is the "crossed" bandage (fig. 1).

A pad of gauze and cotton-wool is placed over the eye, and then the bandage, the end pieces of which are crossed on the occiput and tied on the forehead. It is stated that

the bandage retains its position for twenty-four hours, even in bedridden patients. A bandage 8 to 10 cm. in breadth and 120 cm. in length is suitable for the purpose.

The second type of small bandage, the sling bandage (fig. 2), requires a bandage 8 to 10 cm. in breadth and 80 cm. in length.



FIG. 1.—A crossed small bandage.



FIG. 2.—The sling bandage.

The two ends are split leaving a middle part, 8 cm. square, to be placed on the eye. The two upper ends are knotted above and the two lower below the occiput, and are tied together in the centre to prevent slipping. The advantage of this type of bandage is that the gauze and cotton-wool pad cannot slip down, as it may do with the crossed bandage shown in fig. 1.

Referring to the advantages of the small ophthalmic bandages the author states: "Correctly applied they are sure and immovable. A skilfully applied small bandage, with an 80 to 120 cm. swathe, holds more safely and covers better than the monocular bandage used generally".

Cirrhosis of the Liver

AN analysis of the results obtained in a series of 124 cases of hepatic cirrhosis treated by diet, bed rest, abstinence from alcohol, diuretics and supportive care is given by A. J. Patek *et al.* (*Journal of the American Medical Association*, October 23, 1948, 138, 543). The diet, which was rich in protein, consisted of meat, milk, eggs, fruit and green vegetables. Milk was given three times daily with meals and twice between meals. Yeast, in increasing dosage until 25 g. twice daily was reached, was an important item of the diet: those patients who were intolerant to it were given vitamin B complex preparations. Thiamin hydrochloride (5 mg. daily) and unconcentrated liver extract (5 ml. twice weekly)

were injected intramuscularly, and in those cases with severe polyneuritis or mental confusion, thiamin hydrochloride, 100 mg., and nicotinamide, 300 mg., parenterally daily. When ascites was present, fluid up to 2000 ml. daily was allowed, or more in hot weather. Mercurophylline by injection (2 ml.) was given once or twice weekly, and 4 to 6 g. of ammonium chloride in enteric-coated pills daily by mouth. Abdominal fluid was tapped before severe distension occurred. Patients with cholæmia were given slow infusion of dextrose 10 per cent., 2 to 3 litres in twenty-four hours, thiamin chloride, 100 to 150 mg., nicotinamide, 300 to 400 mg., and riboflavin, 100 mg., being added to the infusion. This treatment was continued until the patient could take oral feeding. Hæmatemesis was treated with transfusion of whole citrated blood by slow drip, and intercurrent infections with sulphonamides. Of the 124 patients treated, 61 showed evidence of improvement: disappearance of ascites, jaundice and œdema, gain in weight and strength, and improvement in hepatic function tests. Estimation of the duration of life after the onset of ascites in 115 treated cases and 230 controls showed: at the end of one year 65 per cent. of treated patients were alive compared with 39 per cent. of controls; at the end of two years 50 per cent. of treated patients, and 21 per cent. of controls; at the end of five years 30 per cent. of treated patients and 7 per cent. of controls. In conclusion it is stated that "Laënnec's cirrhosis is not, of necessity, a progressive disease. With early diagnosis and early institution of treatment the prognosis should become more favourable".

Calciferol and Tuberculous Glands

At the Lord Mayor Treloar Cripples' Hospital, Alton, tuberculous glands are treated by a combination of conservative treatment and surgery, the aim being to obtain healing and quiescence of the glands and then to remove them surgically. Recently this procedure has been supplemented by calciferol, and a report has now been published of the results obtained in twenty-three children and eleven adults who have received calciferol (S. Gauvain, *Tubercle*, November 1948, 29, 259). The dosage given to children was 100,000 units of vitamin D daily, chiefly in dry tablet form; adults received 150,000 units daily. In ten children and two adults the first effect of calciferol treatment was a flare-up of the local condition. This was followed by increased calcification of the glands and decreased peri-adenitis. Of the fourteen children with sinuses, eleven responded well, healing occurring in one to three months. Of the

six adults with sinuses, three healed within three months, two within six months, and one in twelve months. The administration of calciferol was accompanied by a rise in the serum calcium to 13-16 mg. per cent., and in the sedimentation rate. Mild toxic symptoms were noted in nine children and two adults, whilst two children and one adult had moderately severe reactions, and one severe reactions. The earliest toxic symptom was constipation; this was followed sometimes by nausea, vomiting and anorexia. In adults, thirst and polyuria were sometimes present. Renal efficiency tests were carried out in thirteen children, and four showed temporary renal impairment. The advantages claimed for calciferol are that "it speeds up treatment, quiescences occur more quickly, and therefore surgery may safely take place at an earlier stage. The actual surgical excision is greatly facilitated by the calciferol, as the glands are so discrete and well calcified". It is therefore suggested that the important rôle of calciferol is as an aid to surgery and that it will be most useful in the treatment of such cases as out-patients.

Milker's Eczema

MILKER'S eczema is defined by S. Epstein (*Journal of Allergy*, September 1948, 19, 333) as "a fairly common chronic eczema of the hands occurring in farmers or in other people who milk". In a review of 42 cases he describes the main clinical features and the treatment. It consists of a sharply outlined chronic itching dermatitis of the hands, involving chiefly the radial side of the right index finger and the dorsum of the right thumb, and extending on to the radial aspects of the wrist. Whilst it may also involve the left hand, in the author's experience it has always originated on the right hand, usually the thumb. It is usually worse in winter. The localization of the condition is attributed to the fact that this is the part of the milker's hand which rubs against the udder of the cow during milking, and the preference for the right hand is ascribed to the fact that this hand is used more frequently in milking, and that as the right hand is usually stronger and exerts more force there is more severe rubbing against the udder. There are also specific factors responsible for the condition, the main one being sensitivity to cattle. The ideal treatment is to avoid milking. The more acute cases are treated as any other acute dermatitis. In resistant chronic cases 5 per cent. coal tar in zinc ointment or Wilkinson's ointment ("ung. sulfur. compos. U.S.P.") diluted with equal parts of boric acid ointment or Lassar's paste is useful.

REVIEWS OF BOOKS

The Practice of Endocrinology. EDITED BY RAYMOND GREENE, D.M., M.R.C.P. London: *The Practitioner Textbooks*; Eyre & Spottiswoode (Publishers) Ltd., 1948. Pp. xix and 366. Plates 53. Figures 19. Price 52s. 6d.

THIS book is intended primarily for the general practitioner, who will find it most useful for reference. It supplies in a readable form the essentials of a difficult and rapidly changing subject, and at the same time clears away a lot of cobwebs and rubbish that seem to encumber the minds of certain authors of books on endocrinology. Its appeal, however, will not be restricted to the general practitioner, and many students will be grateful for the short and simple chapters on diabetes mellitus, calcium metabolism and adiposity, although they may prefer to read less detailed accounts of pituitary and adrenal disorders. These last-mentioned sections are in many ways the best in the book and give such an admirable and authoritative account of their subject that general physicians and those especially interested in endocrine disorders will wish to read and subsequently make reference to them. The book is really well produced and the illustrations are of high quality: they have been carefully selected and show clearly the points they wish to make. The inclusion of a few reproductions of prints and portraits reminds us that although endocrinology is a comparatively new branch of medicine, sufferers from endocrine abnormalities have always interested their fellow men. This book will give real service to the general practitioner and be a valuable addition to his bookshelf, as well as to that of the student and general physician.

Cardiology. BY WILLIAM EVANS, M.D., D.Sc., F.R.C.P. London: Butterworth & Co. (Publishers) Ltd., 1948. Pp. xi and 310. Figures 269. Price 35s.

THIS book has all the merits of the Mackenzie tradition, and also its demerits. Sound, clear and concise, it is a model of how a textbook should be written. With this book as his guide the student will not go far wrong, whether he be working for a qualifying examination or for a higher degree or diploma. But, he will need to appreciate that some of the views expounded are personal ones which may not be generally accepted. To dismiss "physical examination" in three pages, while devoting four to electrocardiography and five to radiography, is scarcely the physician's approach to clinical medicine. Percussion "as a means of determining the size of the heart may be described as

obsolete" in cardiac departments, but this is not feasible advice for the general practitioner. Throughout the book the emphasis is all upon structure rather than function. The physiological approach is eschewed for the pathological, e.g., the section on "simple hypertension", in which etiology is not even mentioned. In the section on "streptococcal endocarditis" (*alias* subacute bacterial endocarditis), the whole problem of penicillin therapy is dismissed in three sentences. Finally, even the non-psychologist reviewer must be allowed to register a protest against the reference to neurosis in the last paragraph of the book. On the other hand, the merits of this work far outweigh the demerits. This is a book which has come to stay and which will be a standard English textbook on the subject for many years to come. As the personal testament of one of our leading cardiologists it will certainly receive the attention it deserves.

Textbook of Genito-Urinary Surgery. EDITED BY H. P. WINSBURY-WHITE, M.B., Ch.B., F.R.C.S., F.R.C.S.Ed. Edinburgh: E. & S. Livingstone Ltd., 1948. Pp. xv and 1046. Figures 451. Price 90s.

MR. WINSBURY-WHITE aided by a team of no less than 39 authors has succeeded in moulding together a very important tome on urology. The publication of a book of this magnitude on the surgery of the urinary tract and the male genital system is particularly opportune, for urology in this country is in the process of firmly establishing itself as a specialty and attracting promising young men to its fold. The work is an outstanding contribution to the subject and is beautifully produced, yet, in spite of its size, it just fails in being comprehensive. For example, in the chapter dealing with operations on the kidney the emphasis is on the approach to the organ, and only two specific procedures, pyelotomy and nephrectomy, are described. But if the reader turns to the chapter on hydro-nephrosis to ascertain the details there for the conservative operations for that condition, he will find these insufficiently described although the subject is otherwise well outlined. Again, some matters of importance appear to have been overlooked: thus, epispadias is merely mentioned in connexion with development and etiology, although hypospadias is fully described. On the subject of prostatic obstruction and the different methods of operative treatment, the Editor has allowed the exponent of each of the methods to describe his favourite procedure and in his own commentary on this matter wisely reminds us

that "in the hands of a surgeon who has patiently worked to understand and overcome difficulties a particular technique becomes a success when it is often a failure in the hands of others". In spite of some shortcomings, however, the book will rank as the standard one of British urology and should be in the possession of every urologist as well as every surgeon who assays the surgery of the genito-urinary tract.

A Surgeon's Guide to Local Anaesthesia. By C. E. CORLETTE, M.D., CH.M., F.R.A.C.S. Bristol: John Wright & Sons Ltd., 1948. Pp. xi and 355. Figures 200. Price 35s.

This is a most useful book written by a surgeon for surgeons. The author, after prolonged trial and experience, has become a firm believer in local anaesthesia and an enthusiastic exponent of the art of administering it. He stresses its safety, reliability, wide applicability and its shock-preventing qualities. He describes in detail the methods which he himself has found useful, and lays particular stress on premedication, the correct use of adrenaline and the importance of a thorough knowledge of surgical anatomy. The illustrations are excellent, and the book is beautifully produced. It can be thoroughly recommended as a sound, helpful and complete treatise on the subject.

The Modern Management of Gastric and Duodenal Ulcer. EDITED BY F. CROXON DELLER, M.D., M.R.C.P. Edinburgh: E. & S. Livingstone Ltd., 1948. Pp. 227. Figures 57. Price 20s.

ON the whole the Editor and his collaborators have achieved their object of giving a balanced account of the diagnosis and treatment of peptic ulcer. The modern tendency to show more latitude in dietetic therapy has, however, already largely and justifiably supplanted the more austere Hurst regime advocated in this book, and the use of gastric aspiration as a complement to the Hurst diet is open to the criticism that the passage of the tube and general disturbance of the patient may well induce a still greater flow of gastric secretion. The section on the treatment of perforation is definitely heterodox. The opening paragraph "The surgical treatment of perforated ulcer is only an incident, though a major incident, in a full course of medical treatment" conveys, in addition to its sinister *double entendre*, the implication that the old and tried routine of early operation should be replaced by the prolonged and complicated preoperative regime advocated. A general adoption of the author's policy might well result in a "wait to next morning" attitude on the part of overtaxed

emergency surgeons and a consequent deterioration in the mortality statistics of this condition. The modern surgical position is presented by Mr. Maingot and Mr. Monroe in an able critical resumé. The book is beautifully treated.

Modern Treatment of Peptic Ulcer. ASHER WINKELSTEIN, M.D., B.S. London and New York: Oxford University Press, 1948. Pp. xii and 205. Illustrated. 130s.

THE author of this book is best known for advocacy of intragastric drip therapy in treatment of peptic ulcer. His enthusiasm for his own therapeutic offspring naturally colours his outlook, but he gives due consideration to other modern forms of treatment, such as vagotomy, protein hyperalimentation, and terogastrone. Whilst emphasis is laid on treatment, etiology is also discussed. This is a stimulating work which deserves careful consideration by all who are concerned with care of the increasing number of patients with peptic ulceration.

The National Health Service Act, 1946, Annotated. BY S. R. SPELLER, I.C.S. London: H. K. Lewis & Co. Ltd., 1946. Pp. xii, 497 and xc. Price 42s.

INFORMATION on all general aspects of the National Health Service Act, 1946, will be found in this carefully prepared work. A supplementary index has been supplied which gives statutory instruments issued under the provisions of the National Health Service Act, 1946, which were too late for inclusion in the text.

General Cytology. By E. D. B. ROBERTIS, W. W. NOWINSKI, FRANCIS A. SAEZ. Philadelphia and London: W. B. Saunders Company, 1948. Pp. xii and 345. Figures 143. Price 27s. 6d.

TEXTBOOKS on cytology are often shunned by the general medical reader as being too specialized and difficult to follow. There is, however, much general knowledge embodied in this volume which will reward the courageous reader for some insight into the mysteries of the workings of the cell. Of particular interest are the chapters dealing with the submicroscopic organization of the cell, knowledge of which is due almost entirely to the electron microscope. All aspects of cellular activity are given in a comprehensive survey, including the modern treatment of cytogenetics. Genetics has perhaps tended to become a mere plaything of the statistician, and few except the profession

geneticist appreciate the great advances that have been made in the physical interpretation of chromosome changes. This book can be strongly recommended to the more inquiring of medical students and practitioners, and will be eagerly accepted by the professional histologist.

Hemostatic Agents. BY W. H. SEEGER, M.S., PH.A., and E. A. SHARP, M.D., Sc.D. Springfield, Illinois: Charles C Thomas; Oxford: Blackwell Scientific Publications Ltd., 1948. Pp. xii and 131. Figures 27. Price 25s.

THE successful use of hæmostatic agents in surgery involves a knowledge of many of the recent ramifications in the biochemistry of blood clotting. The authors of this monograph have set out to describe the background of recent laboratory work which underlies the clinical uses of these compounds, and also to describe their applications in various branches of surgery. After an introductory chapter on the mechanism of blood clotting, there are accounts of the properties and clinical applications of thrombin, fibrinogen, oxidized cellulose, fibrin foam and gelatine sponge. It is a monograph of practical information, of value both to the student and to the surgeon. For those who are interested in following the subject in more detail a useful bibliography of 370 references is included.

Osteoarthritis of the Hip-Joint. BY H. WARREN CROWE, D.M. London: Rolls House Publishing Co. Ltd., 1948. Pp. viii and 70. Figures 5 and plates 25. Price 35s. 6d.

DR. WARREN CROWE's methods of treatment are well known in this country. His views are on the whole divergent from those of other workers. In this book he describes his concept of osteoarthritis of the hip. It is the result of focal sepsis, it should be treated with vaccines (both autogenous and polyvalent), elimination of the focus, intra-articular injections, physiotherapy, and in certain cases gold injections and dieting. The treatment must be prolonged. It will take at least a year, possibly two, and must be resumed on the slightest reappearance of symptoms. The book is illustrated with many diagrams, photographs, charts and X-rays; some of which, purporting to illustrate improvement, are not convincing. There are also tables showing the results of treatment of patients whose case histories are contributed by members of the staff of the Charterhouse Rheumatism Clinic.

NEW EDITIONS

SECTIONS on the colostrum skin test (prostimine) for pregnancy, artificial insemination, sterility and its surgical and endocrine treatment are included in *A Textbook of Gynaecology*, by Wilfred Shaw, M.D., F.R.C.S., F.R.C.O.G., in its fifth edition (J. & A. Churchill Ltd., 25s.). The book has been completely revised and new illustrations added.

MANY new aspects of orthopædic surgery which evolved during the war years are included in *Handbook of Orthopedic Surgery*, by Alfred Rives Shands, Jun., M.D., in its third edition (C. V. Mosby Company, \$6). The first chapter on neuromuscular disabilities is devoted to infantile paralysis, in which, in addition to general treatment, exercises and splinting, and surgical measures for the correction of deformities are discussed. New methods in the treatment of arthritis, both chronic and infective, are also included. Some of the illustrations, in particular reproductions of drawings of bones, are beautifully reproduced.

MUCH new material is contained in *Hygiene*, by J. R. Currie, M.D., F.R.C.P., D.P.H., and A. G. Mearns, M.D., D.P.H., F.R.C.S.E.D., in its third edition (E. & S. Livingstone Ltd., 35s.). Current legislation on milk and the inspection of dairies and food premises, water supply, housing, aircraft health regulations, the control of infestation, and a concluding section entitled Social Vista dealing with social medicine in all its aspects, including the new National Service Act, are among the features of special interest.

EXTENSIVE rewriting has been undertaken in the preparation of the fifth edition of *A Textbook of Histology*, by Alexander A. Maximow and William Bloom (W. B. Saunders Company, 42s.). The illustrations in the new edition, which total 562, are beautifully reproduced and add greatly to the value of this excellent textbook of histology.

Deep Massage and Manipulation Illustrated, by James Cyriax, M.D., B.Ch., in its third edition (Hamish Hamilton Medical Books, 17s. 6d.) contains among the new material manipulative measures for the reduction of cervical and lumbar discs.

SOME new recipes have been included in *The Diabetic ABC*, by R. D. Lawrence, M.D., F.R.C.P., in its tenth edition (H. K. Lewis & Co., Ltd., 4s.).

NOTES AND PREPARATIONS

NEW PREPARATIONS

"CREMOMERAZINE" sulphamerazine suspension (3 g. sulphamerazine in each 30 ml. [1 fluid ounce]) is stated to be a pleasantly flavoured preparation of easy absorption. In addition to its use in pneumococcal, streptococcal and staphylococcal infections, the prophylactic administration of cremomerazine is advocated for the prevention of recurrences of rheumatic fever. (Sharp & Dohme Ltd., Hoddesdon, Herts.)

DISPARIN tablets each contain 5 grains of acetylsalicylic acid with calcium base sufficient to form, when dissolved in water, a neutral solution containing 6 grains of calcium aspirin. Among the advantages claimed for this preparation are its stability, as the calcium aspirin is not formed until the tablet is immersed in water or other aqueous fluid, and its suitability for administration to children, particularly when massive dosage is required for the treatment of rheumatism. (Reckitt & Colman Ltd., Hull, and 40 Bedford Square, London, W.C.1.)

ETICYCLIN (ethinyl œstradiol) is stated to be "the most potent orally active œstrogen for sublingual administration". It is supplied in the form of linguets of 0.05 mg. for use in the treatment of amenorrhœa, uterine hypoplasia, menopausal symptoms and carcinoma of the prostate. (Ciba Laboratories Ltd., Horsham, Sussex, from whom a booklet on the Ciba hormone preparations can be obtained.)

PERSEDON (3:3-diethyl-2:4-diketo-tetrahydropyridine) is a new sedative and hypnotic which is stated to possess a wide margin of safety and to have practically no side-effects. Its use is indicated in mild and moderate insomnia and for reinforcing the action of more powerful drugs (the dosage of which can thus be reduced) in severe and chronic cases. (Roche Products Ltd., Welwyn Garden City, Herts.)

ANAHÆMIN B.D.H.—The manufacturers of this preparation have succeeded in isolating from it an antipernicious anæmia factor (A.P.A.) which is probably identical with vitamin B₁₂. This factor has been found to be active in minute doses for the production of, normal erythropoiesis and in arresting the progress of subacute combined degeneration of the cord. (The British Drug Houses Ltd., London, N.1.)

B.M.A. SCHOLARSHIPS AND PRIZES

THE British Medical Association invites applications for the Ernest Hart Memorial Scholarship (£200), the Walter Dixon scholarship (£200), and four research scholarships (£150), for research in any subject relating to the causation,

prevention or treatment of disease: also Insole scholarship (£250) for research into causes and cure of venereal disease. Six national prizes (value £25) and 17 regional prizes (£15 and £7) will be awarded to medical students for essays on "The Value of Observation Training of the Medical Student". Inquiries should be addressed to the Secretary, British Medical Association House, Tavistock Square, London, W.C.1. All essays must reach the Secretary not later than March 31, 1949.

SCIENTIFIC FILMS

The Scientific Film Association.—A booklet entitled "On Organizing Medical Film Programmes" (1s.) and a pamphlet "Notes on How to Borrow Films" can be obtained from the Scientific Film Association, 34 Soho Square, London, W.1.

Films of medical interest recently exhibited include:—*The Milky Way* tells the story of milk production, pasteurization and delivery from the farm to the consumer and illustrates the care that is taken to ensure a pure supply. (Applications for loan to the International Relations Officer, United Dairies Ltd., 100 Pall Mall, London, W.2.) *One Man's Story* A Central Office of Information film, telling the story of Dr. G. C. M. McGonigle, Medical Officer for Health for Stockton-on-Tees, 1925-1939. It is available from the Central Film Library, Imperial Institute, Kensington, S.W. *Emulsions and Fish to Capsule* are new films produced for the Crookes Laboratories Ltd., Park Royal, London, N.W.1 to whom inquiries for these and other films should be addressed.

PUBLICATIONS

Pamphlet on Dyspepsia.—Reprints of the pamphlet "Notes on the Nature and Treatment of Indigestion" appearing on pp. 53-60 of issue can be obtained from the Publisher, *The Practitioner*, 5 Bentinck Street, London, W.1, at 6d. each, or 10 for 4s. 6d. and 5 for 1s. 6d. post free.

The Role of Folic Acid in Nutrition and in Common Forms of Anæmia, a well-produced booklet with colour plates and bibliography available on application to Cyanamid Products Ltd., Brettenham House, Lancaster Place, W.C.2. *Estimation of Sulphonamides and Sulphonamide Therapy*, booklets published by May and Baker Ltd., Dagenham, Essex, the first in its series, can be obtained on application.

The contents of the February 1949 issue, which contain a symposium on "Cardiovascular Disease", can be found on page lxxviii at the end of the advertisement section. An index to advertisements appears on p. li.

THE PRACTITIONER

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THE TREATMENT OF ANGINA PECTORIS: WITH SPECIAL REFERENCE TO DRUG THERAPY

By P. T. O'FARRELL, M.D., F.R.C.P.I., D.P.H., D.T.M.

*Visiting Physician, St. Vincent's Hospital, Dublin; Consulting Cardiologist,
St. Kevin's Hospital, Dublin, and to the British Ministry of Pensions, Dublin.*

THERE is no doubt that psychogenic reactions are of considerable importance in patients suffering from angina pectoris. The physician should therefore endeavour to evaluate the nature of these reactions by a detailed examination of the patient's history, habits and emotional responses. In most instances it is necessary to allay fear, to reassure the patient and to maintain a reasonably optimistic outlook. The term angina pectoris should be used sparingly, if at all, but the patient should be told that the arteries of his heart are not acting properly and that care will be needed to keep them up to the mark. Obviously the individual patient will have to be treated according to the stage of the disease, but there are some general considerations which are applicable to all cases.

GENERAL MEASURES

In typical angina pectoris it can safely be assumed that three causal factors are operating either independently or collectively. These are:—(1) Disease of the coronary arteries themselves; (2) vasomotor disturbances of the coronary vessels; (3) extrinsic factors affecting the coronary flow.

As regards the first factor, this is invariably present if the patient is suffering from typical anginal attacks. No drug can directly influence or alter established pathological changes in the walls of the coronary arteries: all that can be done is to encourage the development of a compensatory collateral circulation. This, fortunately, is not unattainable, because there are many examples on record, confirmed by autopsy findings, in which a compensatory vascular mechanism has made up for interference of the blood flow through obstructed coronary arteries. In any given patient it is difficult to decide the degree of coronary involvement, but a careful family

and personal history will often give some indication of the duration and progress of the disease. Coronary disease has a marked familial tendency, and the mode and expectation of life in one member of the family often closely approximate that of another member suffering from the same complaint.

Rest.—The chief means, apart from surgical ones, for promoting a collateral circulation is the utilization of rest, both physical and mental. The amount of physical rest required is partly governed by the patient's emotional make-up. In the angina of rest, bed rest is an indispensable necessity. In the angina of effort, physical activities should be restricted. In some patients a short period of bed rest is often desirable provided some assurance is given that this will only be a temporary measure. Some patients, however, owing to financial, business, or family commitments, are often unwilling to limit their activities and then some *modus operandi* must be evolved. They should lead a more orderly form of life and cut down the extent and speed of their mental and physical activities. Mental tasks should be undertaken only when the mind is fresh and cease if weariness comes on. They must also learn to curb their emotional reactions. Periods of rest and relaxation during the day, particularly after meal times, are usually desirable. In other patients a leisurely holiday is often of great benefit. Adequate sleep must also be assured and the bowels regulated.

Weight reduction in stout subjects undoubtedly helps to lessen the strain on the heart and to make reduced demands on the coronary circulation. Weight reduction should be brought about slowly by modification of the diet and graduated exercises. Reducing drugs should not be used. Those who are accustomed to heavy meals should turn to lighter and less generous fare. An abdominal belt is sometimes of benefit in those who are corpulent.

Although the effect of *tobacco* on the coronary circulation is not fully understood, there is no doubt that some patients with angina pectoris improve when they stop smoking. The use of tobacco should in all cases be greatly restricted, if not abandoned. *Alcohol* in moderation appears to be of benefit in some cases.

Drugs will not have any direct effect on diseased coronary arteries, but they can play a useful part in controlling vasomotor disturbances of those arterial branches which are not too extensively involved in the disease process. Coronary vasodilatation is not only necessary for the symptomatic relief of pain, but it also helps to open up collateral channels.

FACTORS PRECIPITATING ATTACKS

Vasomotor disturbances of the coronary vessels are brought about through reflex vagal stimulation or possibly through failure or inhibition of normal sympathetic vasodilator tone. These conditions may produce a disproportion between the coronary supply and the heart's needs, but seldom give rise to true angina pectoris unless the coronary flow is already restricted by

disease. A common cause of reflex vagal stimulation is overdistension of the stomach after a full meal, a condition which often precipitates an attack of angina pectoris. The importance of spasm in the production of anginal attacks is supported by experimental evidence: for instance, artificial distension of the stomach in dogs causes a marked decrease in the coronary flow, which does not take place if the vagi have been cut or atropine administered beforehand. A well-known clinical phenomenon is that patients often claim that "gas in the stomach" brings on an attack of angina pectoris and that if they bring up the gas the attack stops. Reflex autonomic stimuli may arise from a variety of abdominal conditions: for instance, experimental distension of the common bile duct in man will produce anginal pain, and similar symptoms are frequently encountered in peptic ulcer and hiatus œsophageal hernia.

Extrinsic conditions may produce anginal attacks by disturbing the physiological balance between the coronary supply and the demands of the heart. As the coronary flow is at its peak during diastole of the heart, any excessive fall of pressure during this period or any shortening of the period itself may result in an inadequate supply of oxygen to the myocardium, particularly if the heart is called on to increase its output. Thus the low diastolic pressure of aortic regurgitation may reduce the force of the coronary circulation, although this is sometimes compensated by an increased elevation of the systolic pressure; but failure of this compensatory mechanism may initiate an anginal attack. In severe anæmia, apart from the low diastolic pressure, the heart muscle suffers from a relative anoxæmia with the rest of the body. Polycythæmia may produce anoxæmia owing to oxygen unsaturation, an increased number of cells and increased viscosity. In paroxysmal tachycardia the rapid heart action may call for a greater coronary flow than can be delivered. In hyperthyroidism the increased metabolic rate requires a faster blood flow and an increased output volume of the heart. In cardiac hypertrophy there may be impairment of the nutrition owing to the increased amount of thickened tissue to be nourished.

In all these conditions the cardiac work may exceed the coronary supply and thus play a contributory part in the production of anginal attacks. It should be noted, however, that some of these conditions are open to correction or amelioration with appropriate therapy.

DRUG THERAPY

The drug treatment of angina pectoris centres mainly in the treatment of individual attacks and the therapeutic measures to be taken to diminish the frequency and severity of future attacks. It is convenient to classify these drugs according to their main pharmacological actions.

Sedatives and hypnotics.—Many patients with angina pectoris need sedation of some kind, not only on account of their emotional make-up, but also to render them amenable to an altered mode of life. Sedatives such as

sodium bromide, 15 grains (1 g.) t.i.d., or phenobarbitone, $\frac{1}{2}$ a grain (32 mg.) t.i.d., will tend to produce mental tranquillity and lower nervous receptivity. These drugs can be given over long periods, but the danger of intoxication should not be overlooked. Some authorities prefer to use one of the bromo-valerian compounds in the form of an elixir.

To assure adequate sleep a wide choice of hypnotics is available. For most patients a quickly acting barbiturate, with rapid clearance, such as seconal or amytal, is the most suitable. For more prolonged effects stable barbiturates, such as medinal or dial, can be used. All barbiturates are capable of producing unpleasant reactions and there is also the danger of chronic barbiturate intoxication.

Vasodilator drugs.—Of these there are two chief groups: (a) those which act quickly and last for only a short time, and (b) those which act slowly and have a more sustained effect.

The first group comprises such drugs as amyl nitrite, octyl nitrite (both administered by inhalation), and glyceryl trinitrate (administered by absorption from the buccal mucous membrane). All these drugs are suitable for the immediate treatment of an acute anginal attack, but it is generally agreed that glyceryl trinitrate (trinitrin) is the best drug. It should be taken in tablet form, dose $1/200$ to $1/100$ of a grain (0.32 to 0.65 mg.), and the tablets should be fresh, and be slowly chewed. Glyceryl trinitrate has the further advantage that it can be taken prophylactically to ward off anticipated or impending attacks of angina pectoris. There is no harm in repeating the dose several times during the day, particularly in patients suffering from angina of rest, but it should be realized that the therapeutic action rarely lasts for more than ten minutes. Sometimes it is desirable to accelerate the action of the drug either by adding an excipient to the tablet to increase the permeability of the buccal mucous membrane or by administration in liquid form. Respective examples of such preparations are "antipressan" tablets (to be taken sublingually), and "natirose" dragées (to be crushed in the mouth).

The more slowly acting vasodilators with a prolonged action are useful for the treatment of angina pectoris between attacks. They comprise such drugs as erythrol tetranitrate, mannitol hexanitrate, the xanthine derivatives, coramine-adenosine, and papaverine. Erythrol tetranitrate and mannitol hexanitrate ($\frac{1}{8}$ to $\frac{1}{2}$ grain [8 mg. to 32 mg.] tablets t.i.d.) are not suitable for all patients because of unpleasant side-effects such as headaches. Moreover, tolerance may develop with the continued use of some of the nitrate or nitrite drugs. In initiating treatment therefore the smallest effective dose should be employed, so that should tolerance develop the dosage may be increased. It is sometimes useful to alternate these drugs in an intermittent manner.

Of the various xanthine groups of drugs, compounds of theophylline, such as aminophylline (theophylline ethylenediamine), are of undoubted value in

the treatment of angina pectoris. Apart from their diuretic effect there is substantial experimental evidence to show that these compounds do produce coronary vasodilator effects. Aminophylline should therefore be used as a routine treatment over long periods; there is no diminution of effect and no unpleasant symptoms are produced. Aminophylline is much more likely to be effective in cases in which coronary constriction, as opposed to coronary sclerosis, is the main factor in interfering with the blood supply. But even in coronary sclerosis there is often some degree of superimposed vasoconstriction which may be responsible for acute attacks of pain. Aminophylline should be administered orally in enteric-coated capsules, to avoid gastric irritation, and the average dose is $1\frac{1}{2}$ grains (0.1 g.) t.i.d. Some authorities claim that it produces a more pronounced effect when administered in rectal suppositories. Aminophylline is marketed under various trade names such as "cardophyllin", "euphyllin", "glucophylline", and sometimes a barbiturate is incorporated with the drug as a sedative.

The coramine compound, coramine-adenosine, is stated to have a prolonged vasodilator effect on the coronary arteries, without undesirable side-effects on the circulation. The drug may be given in tablet form two or three times a day, preferably after meals for ambulatory patients, and by injection for those who have to rest.

Papaverine hydrochloride, an opium alkaloid, is stated to have the following effects: (a) a mild sedative action, without narcosis, but capable of dulling the sensation of pain; (b) a definite and lasting coronary vasodilator effect, which makes for better coronary irrigation; (c) a wide margin of safety even in large doses, and it is not habit forming; (d) the drug is not a cardiac depressant. It should therefore be used in the routine treatment of many cases of angina pectoris. The usual dose is $\frac{2}{3}$ of a grain (45 mg.) given orally, two or three times a day. Eupaverin, a synthetic compound, is stated to have a stronger spasmolytic effect than papaverine. It may be administered orally in $\frac{1}{2}$ -grain (32 mg.) doses.

ANALGESICS

Apart from the acute pain of an anginal attack many patients with coronary sclerosis complain at times of vague discomfort in the neighbourhood of the præcordium. This discomfort should be kept in check by using one of the milder analgesics. Aspirin with or without codeine is a suitable drug to use, for all the salicylates have a favourable effect on thrombosis by lessening prothrombin activity, that is to say, by producing a dicoumarol-like effect. Another useful analgesic is pethidine hydrochloride (dose 25 to 100 mg.), which is comparatively free from toxic reaction and is stated to have a powerful spasmolytic action.

ANTISPASMODICS

In recent years considerable attention has been given to the effects of

obnoxious reflexes mediated through the vagus in cases of angina pectoris. Many of these reflexes arise from gastro-intestinal sources and this has led to the use of synthetic atropine analogues. These synthetic compounds in general, produce a direct papaverine-like effect on smooth muscle and, being parasympathetic depressants, they act peripherally, through the vagus like atropine. They have a relatively feeble cerebral action and present a favourable ratio of therapeutic potency to toxicity. Their administration does not produce the undesirable side-effects of atropine, such as tachycardia, mydriasis, dryness of the mouth. These synthetic atropine analogues are marketed under trade names such as "novatropine", "trasentin-6H", "syntropan". They can be administered orally or in the form of suppositories.

MISCELLANEOUS MEASURES

Oxygen therapy.—In the angina of rest, oxygen, with other therapeutic measures, sometimes helps to convert a recumbent patient into an ambulatory one. Oxygen is particularly useful for those patients who suffer from dyspnoea and pulmonary congestion.

Cardiac glucosides should not be used in angina pectoris unless there is evidence of congestive failure, or in those rare instances when auricular fibrillation supervenes.

Drugs for the reduction of the basal metabolic rate.—Methyl thiouracil has been used for this purpose, but to be effective it must be given in much larger doses and for a longer period than in ordinary thyrotoxicosis. Before undertaking such treatment, cases must be very carefully selected on account of the danger of thiouracil intoxication.

Vitamin preparations, insulin-free pancreatic extracts, and synthetic hormones, have also been used because of their supposed vasodilator effects. There is, however, no substantial evidence that these drugs are of any real value, although testosterone propionate injections seem, in some indirect way, to benefit some patients. Of the vitamin preparations, tocopherol therapy (vitamin E in large doses) has recently been advocated by some observers, whilst others maintain that this form of therapy is ineffective.

As already mentioned, some patients with angina pectoris suffer concomitantly from other diseases, such as anæmia, peptic ulcer, cholecystitis, thyrotoxicosis and diabetes mellitus. These diseases should therefore be treated on conventional lines, but in cases of diabetes it is better to avoid insulin medication if at all possible, for a state of mild hyperglycæmia is preferable to one of hypoglycæmia.

SURGICAL TREATMENT

Surgical treatment of angina pectoris should be reserved for patients who after adequate observation cannot be controlled effectively by medical means. Surgical operations can be divided into two main groups: (a) those

designed to open up new collateral channels, and (b) those primarily intended for the relief of pain. The first group comprises such operations as total thyroidectomy, grafting of intercostal muscle to the myocardium, and cardio-omentopexy. These rather formidable procedures seem to have gone out of fashion in recent years. The second group includes such operations as posterior rhizotomy, ganglionectomy, and paravertebral block with alcohol. Patients with a fair cardiac reserve may be subjected to posterior rhizotomy, particularly when the reference of pain is bilateral. For the more questionable risks thoracic ganglionectomy is preferred, especially if the anginal pain is unilateral. For the poorest risks with great reduction in cardiac reserve paravertebral block with alcohol is advised.

These operations, designed for the relief of pain, are sometimes criticized on the grounds that by relieving pain they remove the vital danger signals which warn the patient that he is overtaking his heart. Practical experience, however, shows that the relief of pain has a favourable influence on the coronary flow and tends to promote the establishment of the collateral circulation. Surgical intervention should probably be considered more often when an adequate medical regimen fails to control severe and prolonged anginal pain. These measures may in some instances ward off the onset of coronary infarction.

CONCLUSION

The future of a patient with angina pectoris depends in a measure upon his ability and willingness to live within the limits of his disability and in part upon his emotional make-up. Whilst it is often hazardous to venture a prognosis in any individual case, it is well to remember that angina pectoris is by no means so grave a condition as was previously thought. Sudden death is not necessarily a consequence of angina pectoris, and this should encourage a more optimistic outlook.

CARDIAC ŒDEMA: CAUSATION AND TREATMENT

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ŒDEMA is but one of the signs of congestive heart failure, yet it often dominates and deserves special attention. Only systemic œdema will be discussed here, for pulmonary œdema is a subject to itself. Cardiac œdema is found mainly in dependent parts because the already raised venous pressure in them is increased by the hydrostatic pressure of the venous column of blood. This effect of gravity is not nearly so important in other types of œdema.

CAUSAL FACTORS

Raised venous pressure.—Experimental observations by Landis (1930) on tissue fluid exchange, indicate that the pressures in capillary loops are, at the arterial end, 32 mm. Hg, at the venous end, 12 mm. Hg, and midway, 20 mm. Hg. According to Fahr (1941), if the venous pressure is increased above the normal of 5 mm. Hg, to 13 mm. Hg or more, the osmotic pressure of plasma protein, 22 mm. Hg, is not enough to prevent fluid from leaving the capillaries, and œdema forms. This is what happens in congestive heart failure. Simple venous stasis from immobility of the lower limbs aggravates the œdema and represents an increased pressure of as much as 10 to 50 mm. Hg (Smirk, 1936). As the arms are relatively active even in very ill cardiac patients, in them dependent œdema is not often marked even when the general venous pressure is very high, but the breasts may reveal much œdema. It is the raised venous pressure occasioned by stasis that is the important factor and not simply reduced blood flow, for œdema is not seen in ordinary peripheral circulatory failure. *Defective lymphatic drainage* also figures in the production of cardiac œdema. Raised venous pressure in the great veins of the neck dams back lymph from the thoracic duct.

Chronic œdema may be increased by *abnormal capillary permeability* caused by capillary malnutrition or even by separation of cells. Protein leaks out and tissue retention of œdema is promoted. A study of œdema fluid shows that it contains 0.1 to 0.5 g. per cent. (Fahr, 1941), which is surprisingly low and argues against much capillary damage. Yet in some of my patients with very long-standing œdema there was a rise in the protein content of œdema fluid from 0.6 to 1.4 g. per 100 ml. as the months passed, but the specific gravity remained under 1.010. Retention of metabolites raises the osmotic pressure of tissue fluid and resorption is thereby hindered. Occasionally, anæmia contributes materially to œdema of heart failure, mainly by virtue of diminished plasma protein. A low plasma protein may

also be due to poor intake, to defective function of a congested liver, or to loss of albumin in urine or effusions when evacuated. Fahr (1941) considers that a fall of blood colloidal osmotic pressure of 7 mm. Hg is equivalent to an 8 mm. Hg rise of capillary pressure. An augmented blood volume, as found in some cases of mitral stenosis or emphysema with polycythæmia, aids œdema formation.

Another factor which has been much studied recently is *disturbance of sodium ions*, but the importance of salt in the genesis of œdema has been known since the beginning of this century (Vaquez and Laidlaw, 1924). When sodium chloride is excessive in the blood stream, the blood volume is increased and œdema formation is facilitated. Such excess may be caused by salt in food, and by impaired excretion of salt by kidneys made inefficient by reduced cardiac output and by congestion, although renal failure is not otherwise apparent. Regulation of salt in the diet is therefore important. Vitamin B₁ deficiency rarely occurs in chronic cardiac failure and results from over-strict dieting.

The reasons for œdema not becoming gross in every case are that the counter-pressure of the œdema fluid outside blood vessels decreases the rate of transudation of fluid, and that the several œdema-producing factors do not all operate in one individual, although raised venous pressure and sodium retention always dominate.

DIFFERENTIAL DIAGNOSIS

The detection of cardiac œdema is easy when the characteristic pitting occurs. But from 5 to 8 litres of fluid may be retained in large persons before this feature is apparent, and it is computed that the limb volume increases 10 per cent. before pitting occurs. Cardiac œdema is generally tender. It may just be detected under the soles of the feet, behind the malleoli or on the shins. In more advanced cases redistribution of the œdema is often mistaken for its disappearance when the patients take to bed. It is wise to look at the back of the thighs as well as the sacral area.

A few simple guides help in the differential diagnosis of cardiac œdema. Shortness of breath is always noted on exertion and is roughly proportionate to the extent of the œdema, if due to a failing heart. Exceptions are extremely rare, and this simple rule prevents mistakes in diagnosis of œdema from portal obstruction in hepatic cirrhosis or thrombosis of the inferior vena cava or both femoral veins. Chronic cardiac œdema is very seldom found in the absence of cardiac enlargement, which may need checking radiologically. An important exception is constrictive pericarditis. The general venous pressure is persistently raised if the œdema is due to heart failure. A hypertensive woman may complain of swelling of the legs, and too often in this type of patient congestive failure is diagnosed when anæmia, obesity, varicose veins, flat feet or even pelvic tumour are responsible for the œdema.

Renal œdema is as a rule characteristic, yet there are cases of nephrotic œdema in the middle-aged which simulate cardiac œdema very closely when the face is not affected. Gross albuminuria, disproportionate to that found in cardiac failure, should prevent mistakes. A heavy cloud of albumin may be seen in heart failure, but seldom more. Shortness of breath will be absent or less than expected in relation to the gross œdema, unless hydrothorax is present. In *heart failure* the kidneys are simply congested, and treatment, including perhaps a venesection, may relieve them and permit diuresis. Dropsy may become very chronic. It is notable that some patients remain ambulant despite large œdematous legs, and they are often less disabled than others who persist with cardiac asthma and great dyspnoea on exertion. Perhaps the œdematous legs act as temporary fluid reservoirs which reduce the blood volume, thus limiting the work of the heart. Rest then causes a diuresis. Others have prominent ascites, yet never develop hydrothorax; others have hydrothorax as the main collection of fluid. Congestive cardiac failure, rare enough in young children, seldom causes much œdema in them, perhaps because the liver distends readily and to a very great degree, thus acting like a venesection. When failure has been treated and the general condition is much improved, yet much œdema persists, then *venous thrombosis* is a possible cause which is not suspected often enough.

GENERAL TREATMENT

Rest in bed.—Whatever the etiology of the heart disease, and irrespective of rhythm, rest may cause a diuresis and disappearance or reduction of œdema, but if total treatment of an adult does not achieve loss of all œdema and there is no active heart disease, simply a gradual failure, he may be allowed up after six or eight weeks and so avoid complete invalidism. Such patients are able to get about a little and their existence is usually tolerable. Odd days in bed, however, do much good and should be encouraged.

Diet.—In acute failure a congested stomach demands only small bland meals, but in chronic failure the rule obtains that there must be a very good reason to preclude any food liked by the patient. Meat, be it red or white, if readily digested without discomfort, does good in providing proteins and vitamins and obviates two contributory causes of œdema.

Salt and fluids.—For many years salt has been restricted in the treatment of cardiac œdema but in recent times more positive proof of its deleterious effect has been obtained, and when salt is sufficiently restricted, fluids can be taken more liberally. A normal diet without salt for cooking probably contains 3 g. of salt daily, whereas 1 g. daily is the amount to be aimed at in congestive heart failure. To this end Schemm (1942) has provided a diet which includes salt-free or salt-poor foods only. It is difficult enough to prepare in hospitals and is impracticable in the home, especially while food rationing persists. It is a method, however, which has a definite place in the therapeutics of cardiac œdema, mainly in the so-called "irreducible"

type. It is, however, known that in many œdematous cardiacs limitation of fluids to 850 ml. (30 oz.) a day and no added salt are sufficient restriction if the help of digitalis and mercurial diuretics is enlisted. Karrell's original diet consisting of only 850 ml. (30 oz.) a day of skimmed milk was successful because it implied restriction of fluids and of salt. It may still be used with benefit for one day each week or at longer intervals if warranted.

PRODUCTION OF DIURESIS

Digitalization is indicated in all types of congestive heart failure whatever the rhythm, except in pneumonia, in very recent coronary thrombosis and, if confirmed, in high output heart failure, e.g. emphysema; but if failure is progressive with other methods of treatment a careful trial of digitalis becomes indicated in these conditions also. In emphysema, ouabain is preferable to digitalis (McMichael, 1948). A diuresis from digitalis can be expected in 45 per cent. of patients in failure with œdema, but it may not be adequate. Only 10.3 per cent. of those in normal rhythm show a dramatic output and 12.5 per cent. in auricular fibrillation, although a higher percentage of benefit from digitalis is obtained irrespective of diuresis (Gavey and Parkinson, 1939). Digitalization is obtained by administration of tablets of digitalis leaves, 0.1 g. (2 grains) t.d.s., for five to eight days, then a maintenance dose of 0.05 g. (1 grain) t.d.s., then b.i.d.; or digoxin, 0.25 mg. q.d.s., for the same period, then 0.25 mg. b.i.d., or daily. Further details regarding digitalization are discussed in another article (see page 105).

Organic mercurial diuretics are of great value but they do not replace digitalis. Both are required, the one acting peripherally, the other centrally. Hundreds of injections have brought relief without untoward effects (Thomson, 1937), and accidents, rare as they are, can be prevented by starting with 1 ml. intramuscularly, then 2 ml. by the same route, followed by 1 ml. then 2 ml. intravenously if no reactions occur. Warning signs are apprehension, tremor and dyspnœa, which may be delayed an hour or more. Mersalyl aids in eliminating sodium from the blood stream and 1 ml. is as potent as a salt-free diet given for several days (Gorham, *et al.*, 1947). Injections may be repeated two or three times a week, if necessary for years. McMichael (1948) claims that mersalyl has an important action on the cardiovascular system besides its well-known effect in limiting resorption from the renal tubules. He states that "when a mercurial is injected without any theophylline, diuresis follows in a period of 4 to 10 hours. At the peak of the diuresis, the venous pressure is reduced and the cardiac output is raised. As the diuresis passes off the venous pressure climbs again towards the value prior to injection. The action is very like that of a venesection. This is the first clear demonstration of a circulatory action of mersalyl, and the value of the substance in the treatment of heart failure is further appreciated".

Ammonium chloride increases mercurial diuresis. Evans (1941) found a single dose of 2 g. (30 grains), in capsules of 0.5 g., two hours before the injection, as effective as the more protracted administration formerly advocated, and the usually small advantage gained by the addition of ammonium chloride does not justify the more elaborate dosage. A vast diuresis is not without danger. Dropsical patients already digitalized have a store of digitalis in tissue œdema, and mobilization of this may precipitate digitalis poisoning. Auto-intoxication by serum protein may also occur if too much tissue fluid is quickly mobilized (Vaquez and Laidlaw, 1924).

Aminophylline is a useful diuretic for intermittent use in slight œdema. A dose of 0.2 g. (3 grains), thrice daily for three days each week, is recommended. More protracted dosage tends to cause gastro-intestinal disturbance and headache, and its effect wears off if given continuously. It is helpful in allowing the patient a temporary rest from injections.

Vitamin C has long been known to have diuretic properties, but much larger doses, up to 2000 mg. daily by mouth for five to seven days, are now used and more pronounced results are obtained. This method is not suitable for general use but is one to be tried in cases of "irreducible" failure. *Vitamin B₁* should be prescribed only when there is reason to expect a deficiency.

Paracentesis.—Removal of hydrothorax or ascites may cause a satisfactory diuresis, and in the later stages of many chronic œdematous cases reliance may have to be placed on routine tapplings every few weeks while the mercurials are continued, if practicable.

Mechanical drainage by Southey's tubes or multiple incisions is not often required since the introduction of mercurial diuretics, but it does give great relief on occasion. Infection is rare and penicillin now affords protection when applied to the skin. A plastic watertight pillow-case placed over the dependent feet serves as an excellent receiver for œdema fluid.

The mercurial diuretics hold pride of place in the newer treatment of cardiac œdema, and whereas chronic anasarca was commonly seen fifteen years ago in heart patients in hospital, it is now rare.

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DIGITALIS AND ITS DERIVATIVES

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SINCE its introduction by Withering as a cure for dropsy, digitalis has come to be regarded as a sovereign remedy in the treatment of cardiac failure but, in spite of continued clinical and pharmacological investigation of its action, unanimity of opinion is still lacking on several issues. There is still doubt, and often difficulty, in choosing a preparation of digitalis for clinical use, and knowledge of the pharmacological action of the digitalis glucosides is still far from complete. Consequently, although the clinical indications for the use of digitalis are fairly clearly defined on empirical grounds, they still lack full pharmacological reassurance.

CHEMISTRY AND SOURCE OF DIGITALIS

Digitalis of the B.P. is the dried leaves of the *Digitalis purpurea*, the common purple foxglove, but a number of plants contain glucosides with similar pharmacological properties. The more important of these are the *Digitalis lanata*, Squill (the dried bulb of the sea onion, *Scilla maritima*), *Strophanthus kombé*, *Strophanthus gratus*, and *Convallaria majalis* (lily of the valley). These plants yield one or more glucosides of complex structure. Each glucoside consists of a combination of an aglucone, a structure of steroid character to which its cardiac action is due, firmly combined with one or more molecules of sugar and more loosely combined with another sugar and acetyl group (table 1). Whilst the aglucone is solely responsible for the

TABLE 1

Crude or native Glucoside	—	Hydrolysis removes Glucose	→	Glucoside	—	Intracellular hydrolysis removes Pentose Sugar	→	Aglucone
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cardiac action of the glucoside, the sugar with which it is combined is thought to effect its speed of penetration of the heart muscle and the firmness with which it remains combined in the muscle cell. As will be seen from table 2 (p. 102), it is possible to prepare a series of cardiac glucosides at various stages of purification.

The terminology of these preparations is somewhat confusing, and the confusion is increased by the large number of proprietary names under which the glucosides and mixtures of glucosides are sold. In comparing the properties of digitalis bodies I shall confine myself to a consideration of the official preparations and the most commonly used substances.

PHARMACOLOGICAL ACTIONS

Digitalis glucosides act mainly on the heart muscle and to a lesser extent on the nervous mechanism of the heart, but little or nothing is known of the fundamental action by which these substances affect the cardiac muscle cell. It appears clear that the glucosides penetrate the heart muscle, and that there the active aglucone is split off from the glucoside to exercise its

TABLE 2

Source	Native Glucoside	Glucoside
<i>Digitalis purpurea</i> leaves	Deacetyldigilanid A Deacetyldigilanid B Gitalin	Digitoxin Gitoxin
<i>Digitalis lanata</i> leaves	Digilanid A Digilanid B Digilanid C	Digitoxin Gitoxin Digoxin
<i>Strophanthus gratus</i>		Ouabain
<i>Strophanthus kombé</i>		Strophanthin K. Strophanthoside
Squill	Scillaridin A	

action on the metabolism and behaviour of the cell. The various glucosides differ from each other in the speed with which this intracellular liberation occurs and on the length of time during which they remain fixed to the cell substance. There is as yet no complete evidence for the belief that any particular glucoside possesses any special or distinct property which cannot be explained by variation in the speed and duration of action.

When digitalis shows its beneficial action in cardiac failure, the improvement in the circulation is associated with a number of circulatory readjustments, but apart from subjective relief the change which is most dramatic and most easily measured is a reduction in heart rate. For this reason it was held for a long time that the cardiac glucosides were mainly of value in the treatment of heart failure with tachycardia, and particularly in auricular fibrillation, and that in failure with normal rhythm the drug was of doubtful value. During the past decade it has become clear that the fall in heart rate produced by digitalis is an associated effect subsidiary in importance to the effect on cardiac muscle, and that the greatest benefit is to be expected when myocardial failure has resulted in venous congestion. The weight of evidence so far available to explain the action of digitalis favours the belief that its effects are brought about by its action on cardiac muscle, and whilst the intimate details of this action are quite unknown, the obvious effect of the glucoside is to shorten and increase the force of cardiac systole. It follows from this that the diastolic resting pause will be lengthened and that the ventricle will thus fill and empty better. Since digitalis does not cause coronary constriction, the increased cardiac output will improve

coronary circulation and the oxygenation of cardiac muscle. It has been shown experimentally that digitalis improves the absolute efficiency of the heart in that the digitalized heart is capable of increased work for a given supply of oxygen. The fundamentally important action of digitalis is to increase the force and speed of systole, and at the risk of over-simplification it may be said that the digitalized failing heart acts as a more efficient pump by drawing blood from the veins and increasing cardiac output. In cardiac failure, digitalis often reduces the diastolic size of the heart. This is not yet fully explained pharmacologically, but it is important to realize that whilst this effect is wholly beneficial to the circulation in the dilated and failing heart, it is harmful when the heart is normal and its chambers of optimum size and capacity, because anything which reduces the diastolic volume must result in a fall in cardiac output.

Action in tachycardia.—The reduction in heart rate often seen after digitalis may be produced in two ways. It is in part due to enhanced vagal activity, and it is not certain whether this action is on the central or the peripheral mechanism. The neurogenic effect is not, however, the most important factor in digitalis action, since marked clinical improvement in congestive heart failure may be brought about without appreciable cardiac slowing, and in the normal heart the degree of slowing produced by digitalis is very slight. In addition, in congestive cardiac failure with tachycardia, the tachycardia is often compensatory for diminished cardiac output and anoxæmia, so that as digitalis improves the circulation the compensatory increase in pulse rate diminishes. In this way the tachycardia may be relieved by direct myocardial action, quite apart from any effect that may be mediated by the nervous system.

Action in auricular fibrillation.—In the tachycardia of auricular fibrillation in which cardiac slowing is a prominent effect of digitalis, the slowing is brought about partly by vagal stimulation and partly by the effect on the heart muscle in increasing its refractory period and in slowing the rate of conduction of impulses from the fibrillating auricle over the junctional tissues. This, together with the reduction in anoxæmia brought about by the improved circulation, reduces the excitability of the ventricle.

The foregoing explanation of the action of digitalis is not, however, universally accepted, as evidence has been adduced by pharmacological experiment (Dock and Tainter, 1930; Katz, *et al.*, 1938), and by clinical experiment on man (McMichael and Sharpey-Schafer, 1944), which suggests that the primary action of digitalis in relieving congestive cardiac failure is not on heart muscle, but on the venous side of the circulation. McMichael and Sharpey-Schafer have shown that in congestive failure a fall in venous and auricular pressure with a rise in cardiac output can be produced both by digitalis and by obstructing the venous return from the legs. They seem to suggest that the primary action of digitalis is to lower venous pressure by rendering some part of the venous network more capacious, so that by decreasing the load on the heart the efficiency of the

heart is improved.

McMichael (1948) has stated that venous congestion in cardiac failure may arise in two ways. First, in myocardial hypertensive or valvular disease, high venous pressure is presumably due to back pressure from an inefficient ventricle. Secondly, in conditions in which the oxygen-carrying power of the blood is reduced, as in anæmia or emphysema, there is an increased cardiac output in response to a demand for oxygen; here the venous pressure is raised to maintain the increased output. He has further shown by accurate serial measurements of venous pressure and cardiac output, that the action of digitalis in these two types of congestive failure is different. In low output failure the action is beneficial. By lowering the venous pressure the cardiac output is increased. In high output failure when the venous engorgement is presumably necessary to maintain output, digitalis, by lowering the venous return, reduces the cardiac output and is harmful to the circulation. Whatever the fundamental explanation of McMichael's findings, it is well established by clinical observation that in heart failure secondary to pulmonary disease, digitalis often does harm.

McMichael has also suggested that ouabain, the crystallized glucoside from *strophanthus gratus*, differs from the other cardiac glucosides in that it acts on cardiac muscle rather than on veins, and may be the drug of choice in cardiac failure secondary to pulmonary disease.

Action in œdema.—Whatever the mechanism, the result of the action of digitalis in congestive cardiac failure is to reduce congestion. In this way pulmonary and systemic œdema are reduced. Systemic œdema in cardiac failure is caused partly by the high venous pressure in small venules and partly by failure of renal function from congestion of the kidney. With the relief of these congestive phenomena, œdema fluid returns to the blood, diuresis ensues, and the body weight falls. In spite of these effects it is often necessary to employ other diuretic measures to supplement the digitalis action and to obtain complete removal of œdema. It is obvious from both pharmacological and clinical evidence that in œdema of other than cardiac origin digitalis will be without effect.

ABSORPTION AND EXCRETION

Digitalis given by mouth is well absorbed, even in the presence of venous congestion of the intestine. The tendency to irritate the stomach, which is common to all digitalis preparations, is reduced if the drugs are given with meals. The glucosides are also absorbed readily through the rectal mucosa, and this route of administration is available when special circumstances justify their use. When digitalis is given orally, a single dose generally produces its maximum effect in about six hours, the time of the onset of the effect depending to some extent upon the size of the dose. When a glucoside is given intravenously, rather smaller doses are required than when the same substance is given by mouth, suggesting that intestinal absorption is not quite complete; but even after an intravenous injection of a cardiac glucoside the action on the heart is not immediate, since time is required for the aglucone to be fixed in the heart muscle. Once fixed, the glucoside is slowly released and slowly excreted, approximately at a rate equivalent to the glucoside content of 2 grains (0.13 g.) of powdered digitalis leaf per day. It is clear that to maintain digitalization it is necessary to continue to

administer approximately this amount. Dissipation of these glucosides is slow and variable, and sometimes the cardiac action of a single dose of digitalis may persist for days or weeks, so that continued administration of digitalis at too high a level will tend to lead to accumulation in the body to toxic levels. If these fundamental facts are borne in mind some of the difficulties encountered in the clinical use of digitalis will be reduced.

In his now classical work, "An Account of the Foxglove and some of its Medical Uses", published in 1785, Withering directed that digitalis leaves should be collected when the plant is flowering, dried and powdered, and used in that form or as an extract, an infusion or a tincture, but sagely adds: "The more we multiply the forms of any medicine the longer shall we be in ascertaining its real dose". This remark is no less pertinent to-day than it was in 1785. It is now known that the action of digitalis is due to a variety of glucosides present in the leaves, and that the galenical preparations are liable to vary rather widely in their content of these labile active principles. Withering seems to have favoured the powdered leaves in doses of 1 to 3 grains (0.065 to 0.2 g.) twice daily, and he said that "about 30 gr. of the powder may generally be taken before nausea commences"—a remarkable approximation to the order of dosage used to-day. Confusion still exists, however, regarding the dosage and method of administration of digitalis, and there are hardly two publications in the English language which offer the same advice.

Dosage.—The cardiac patient requires digitalis for two purposes. First, a large dose to bring his heart under the influence of the drug; then a smaller regularly repeated dose to maintain the effect. This latter dose he may continue for the rest of his life. It is unfortunately not possible to lay down any dogmatic fixed dosage schedule which will meet all requirements, as the individual variation in response to digitalis is very great. One factor in determining this variation is the weight of the patient, and numerous systems of dosage based on body weight have been propounded. It is not always easy to predict the œdema-free weight of an individual patient, and circumstances do not often allow of accurate weighing. The principle should be followed that for full digitalization, $1\frac{1}{2}$ grains (0.1 g.) of powdered digitalis for every ten pounds (4.5 kg.) of body weight will be necessary, so that for a patient of 140 lb. (63.5 kg.) approximately 21 grains (1.4 g.) of powdered digitalis will be required. Individual variation in absorption and response to digitalis is considerable, and accurate weighing of the patient is not necessary. The total quantity may be divided according to the urgency of the case. When no great urgency exists, the dose may be given in 3-grain (0.2 g.) increments at six-hourly intervals over a period of forty-eight hours; thereafter 2 grains (0.13 g.) of the leaf may be given twice in twenty-four hours for maintenance. It must be emphasized that these doses are to be regarded as average, and that somewhat smaller quantities may be required by certain patients. It should be remembered that the optimum dose of digitalis is the dose which will relieve all symptoms of cardiac failure, and not necessarily the largest dose which can be tolerated. In general, the minimum therapeutic dose is about 60 per cent. of the maximum tolerated dose, but in severe heart failure the therapeutic dose may be very near the toxic dose. On account of the latency and the tendency to cumulation in the action of digitalis, it is convenient to see the patient in the morning,

so that the effect of the previous day's treatment may be assessed, and in the light of this information instructions can be issued for the day. When it is desired to bring the patient more rapidly under the influence of digitalis, the initial digitalizing dose may be given over twenty-four hours in six-hourly increments of 9, 6 and 4 grains (0.6, 0.4 and 0.25 g.), and maintenance continued with 2 grains (0.13 g.) twice daily thereafter. In the occasional case of extreme urgency when it is necessary to obtain an effect in a matter of minutes, a purified glucoside such as ouabain or digoxin may be given intravenously: in the case of ouabain, 1/240 grain (0.25 mg.), and of digoxin, 1/60 grain (1 mg.). It is generally not necessary to repeat the intravenous drug, and digitalization may be continued by giving 3 grains (0.2 g.) of the leaf six-hourly until full benefit is obtained.

PREPARATIONS OF DIGITALIS BODIES AVAILABLE FOR CLINICAL USE

Powdered digitalis B.P.—Powdered digitalis is the pulverized dried leaf of *Digitalis purpurea*, standardized as regards potency by bio-assay. It is dispensed as the official tablet of digitalis, containing 1 grain (65 mg.). This is the safest and most convenient method of giving digitalis. The powder is readily, if somewhat slowly, absorbed by the intestine, and is certain in action.

Tincture of digitalis is an active fluid preparation, 10 minims (0.6 ml.) of which is equal in potency to 1 grain (65 mg.) of powdered digitalis. It is reasonably stable, but is inconvenient to handle, and the dose must be measured in an accurately calibrated medicine glass. Patients are often instructed to take a certain number of drops of the tincture, but a drop of fluid varies between one-half and one-third of a minim (0.03 and 0.02 ml.).

Of the purified glucosides there are many preparations, some consisting of mixtures of amorphous glucosides, others of pure single glucosides. These preparations have no particular advantage over digitalis leaf, apart from the assurance of uniformity of action and for the possibility which they afford of intravenous administration in cases of urgency.

Digoxin B.P.—Digoxin is a pure glucoside obtained from *Digitalis lanata*, and of the pure digitalis glucosides it appears to be the substance of choice (Batterman and de Graff, 1947). It is well absorbed from the gastro-intestinal tract, and the maximum effect of 1.5 mg. (1/40 grain) is obtained in four to five hours. As an alternative to powdered digitalis, digoxin may be used as the *Tablet of digoxin B.P.*, 1948. The official tablet contains 0.25 mg. (1/240 grain). An initial dose of 0.75 mg. (1/80 grain) to 1.5 mg. (1/40 grain) is followed by doses of 0.25 mg. at six-hourly intervals until digitalization is achieved. For maintenance, 0.25 mg. to 0.5 mg. daily is usually required. In emergency the glucoside may be injected intravenously. For this purpose 1 to 1.5 mg. in alcoholic solution is diluted in about 10 ml. of saline; with such a dose the maximum effect will be seen in from thirty to sixty minutes. Digoxin is relatively quickly eliminated from the body, and after a single

therapeutic dose the effect generally passes off in about two days. It is convenient to remember that 1 mg. of digoxin is approximately equivalent in potency to 6 grains (0.4 g.) of powdered leaf.

Digitoxin is a pure glucoside isolated from *Digitalis purpurea*, and is the main constituent of "digitaline Nativelle". In the pure form it has been extensively used in America, where it was given in a single full digitalizing dose of 1.2 mg. by mouth followed by 0.1 to 0.2 mg. daily for maintenance. Given in this way it replaced the digitalis leaf almost entirely for a time. Digitoxin is completely absorbed but is rather slower in action than digoxin, and is more slowly dissipated, so that the action of the glucoside is prolonged and, as American experience has shown, there is considerable risk of cumulative poisoning. The dose of digitoxin is approximately one-tenth of the dose of digitalis. Batterman and de Graff (1947) have shown that whilst the daily oral dose of digoxin most likely to result in maintenance is 0.5 mg. (i.e. 1/120 grain), the comparable dose of digitoxin is 0.1 mg. (1/600 grains). The prolonged action of this glucoside is its main disadvantage, and much more care is required in adjusting the dose to the individual patient with digitoxin than with digoxin.

Tincture of strophanthus B.P.—Tincture of strophanthus is prepared from the powdered seeds of *Strophanthus kombé* and assayed biologically so that 5 minims (0.3 ml.) of tincture of strophanthus is equal in activity to 15 minims (0.9 ml.) of tincture of digitalis or 1½ grains (0.1 g.) of powdered leaf. This preparation is slowly and irregularly absorbed, and consequently uncertain in action; there is at the moment no clear indication for its use.

Ouabain B.P., 1948, is a crystallized glucoside obtained from *Strophanthus gratus*. It has replaced strophanthus B.P., 1932, but like it is uncertainly absorbed and is given by intravenous injection only. The action is qualitatively similar to that of strophanthin, but it is more rapidly active and is quickly excreted. The potency of ouabain is twice that of strophanthin, so that the dose is 1/500 of a grain (0.12 mg.) to 1/240 of a grain (0.25 mg.). If intravenous treatment with ouabain is considered necessary, a full effect may be obtained by injecting intravenously 1/240 of a grain (0.25 mg.) twice in twenty-four hours, and continuing with a daily injection of 1/500 of a grain (0.12 mg.) thereafter. Ouabain seems to have little advantage over digoxin, but McMichael (1948) has presented evidence which suggests that the glucosides of strophanthus differ in action from the digitalis glucosides in that they cause an increase in cardiac output without affecting the venous pressure, and suggests that they may have a special field of usefulness in the treatment of cardiac failure secondary to pulmonary disease, in which the rise in venous pressure is necessary to maintain a high cardiac output.

The intravenous administration of the digitalis glucosides has a certain dramatic appeal, but the procedure is not without danger and should not be entered upon lightly. It is seldom necessary to obtain a full digitalis action within four hours, and it should always be borne in mind that patients vary much in their reaction to these glucosides; if a considerable

dose has been injected and proves to have been too large, little can be done to remedy the error. This method of administration should be reserved for cases of extreme urgency. Special caution is necessary if a patient has been taking digitalis within two weeks of the emergency. In this circumstance the glucosides should be given in half the quantities usually recommended.

INDICATIONS FOR THE USE OF DIGITALIS

The outstanding indication for the use of digitalis is the presence of *congestive cardiac failure* from myocardial insufficiency. It is unimportant whether the failure involves the whole heart or is mainly of the right or of the left side. It has already been emphasized that the presence or absence of tachycardia does not modify the usefulness of digitalis, and similarly, abnormalities of rhythm do not affect the decision to use digitalis. Since the glucoside acts on the cardiac muscle, the main factor in determining the response of the heart is the myocardial reserve, in that the muscle cell must be capable of responding to the chemical stimulus of the glucoside. It is well recognized that digitalis produces its greatest benefit in congestive heart failure secondary to hypertension, with or without auricular fibrillation. In congestive failure from this cause the cardiac muscle is, for a time at least, physiologically intact and capable of responding to a pharmacological stimulus. When the muscle cell is seriously damaged, as in acute rheumatic carditis in children, the response to digitalis is often disappointing. In failure secondary to cardiovascular syphilis, especially with aortitis, digitalis may often produce little or no benefit. Similarly, when failure results from the action of a toxin on the myocardium, as in diphtheria or typhoid fever, digitalis is ineffective. In the peripheral circulatory failure of "shock", as in pneumonia and other severe infections, the mechanism of failure is not related to the myocardium and digitalis may do harm. Cardiac failure in thyrotoxicosis, myxœdema and in beri-beri is allied in nature to toxic myocarditis, and is not usually favourably influenced by digitalis.

Auricular fibrillation.—Until recently auricular fibrillation was thought to be the cardinal indication for the use of digitalis, but the drug will only produce benefit if the fibrillation is accompanied by congestive failure. When this is so, digitalis treatment is often dramatic in its effects, the congestion is relieved and the heart slowed, but sinus rhythm is not restored and the heart continues to beat irregularly except in those cases in which the irregularity is caused by the congested auricle. In fibrillation of the auricles without failure there is no indication for digitalis, and when the arrhythmia arises as a result of toxæmia, digitalis will only do harm.

Auricular flutter.—The considerations which apply to the treatment of fibrillation apply equally to the treatment of flutter, but the effect of digitalis on the cardiac rhythm is difficult to predict. If failure is present the ventricular rate is usually slowed, but the rhythm may be converted to fibrillation by large doses of digitalis. If congestive failure is relieved and the ventricle slowed, the effect is wholly beneficial, irrespective of the final rhythm.

Paroxysmal tachycardia.—The use of digitalis in paroxysmal tachycardia requires caution. If the tachycardia is supraventricular in origin the action of digitalis on the vagal mechanism of the heart, may cut short an attack, but if the tachycardia originates in the ventricle, digitalis may do harm by increasing the irritability of the ventricular muscle. If electrocardiographic examination is not available, it is safer to try carotid sinus pressure, acetyl- β -methylcholine or quinidine sulphate.

Coronary thrombosis.—The indication for digitalis in coronary thrombosis is the development of congestive cardiac failure. For some days after the acute episode the dominant clinical picture is usually that of shock, for which digitalis is useless. The danger of increasing the force of systole of the infarcted myocardium, or of initiating ectopic rhythms in a ventricular muscle rendered irritable by infarction, has been stressed, but these reasons are outweighed by the advantages to be obtained from digitalis if congestive cardiac failure supervenes. There is no evidence that digitalis causes constriction of coronary vessels but rather that it favours the nutrition of the heart muscle by shortening systole and increasing cardiac output.

Angina pectoris.—There is no evidence that digitalis influences the course of ischæmic failure consistently, and the decision to use digitalis must depend upon the presence of congestive failure. If there is an element of congestive failure, digitalis may improve the nutrition of the myocardium by increasing cardiac output, but in the absence of venous congestion the opposite effect may be produced.

Pneumonia.—The circulatory failure which develops in pneumonia is due to anoxæmia and toxæmia, and there is no indication here for the digitalis glucosides. All the evidence suggests that when digitalis is used routinely in pneumonia, the mortality is somewhat increased. Only in rare cases complicated by congestive failure does digitalis find any place in treatment.

Diphtheria.—In diphtheria the cardiac muscle is damaged by the toxin, and the cardiac glucosides may increase the damage. If congestive failure develops as a complication, great caution is necessary in the use of digitalis bodies; they should be given in doses smaller than the usual digitalizing doses.

Cor pulmonale.—In its chronic form this condition is characterized by increased cardiac output and hypertrophy of the right ventricle which is secondary to obstruction of the pulmonary circulation. The signs of venous congestion in the systemic circulation are late in appearing and are secondary to anoxæmia and the increase in cardiac output. Digitalis is as a rule not helpful in this type of failure, but it has been suggested (McMichael, 1948) that strophanthin or ouabain, by acting mainly on the ventricular muscle and less on the veins, may be the glucosides of choice for these cases.

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THE USE AND ABUSE OF THE ELECTROCARDIOGRAPH

By WILLIAM EVANS, M.D., D.Sc., F.R.C.P.

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THE electrocardiograph has changed much in forty years, both in device and design. The machine which once tested patience and ingenuity in combating electrical interference and overcoming photographic difficulties, has developed into an instrument which is reliable and easy to work. Indeed, the direct writing cardiograph has robbed the test of any anxiety in taking the record, and it has added the valuable facility of electing successive chest leads as the cardiographic examination proceeds, lead by lead.

The purpose of electrocardiography has also broadened since the time it was used largely for research work, or to explain an arrhythmia whenever this incited the curiosity of any doctor. To-day, its scope is such that the cardiological examination of any patient is incomplete if it does not include a cardiogram. The warning must be issued early, however, that diagnosis must never rest on this alone, and it should not be opined in the absence of an appraisal of the patient's symptoms and physical signs. The electrocardiogram must be regarded as a rightful appendage of the patient, so that its peculiar pattern should never be analysed separate from a study of the whole. A projected postal service for the interpretation of electrocardiograms should draw even sterner condemnation; the passage of tracings of interest between friendly observers is meritorious only so long as the patient's treatment is not governed by graphic interpretation offered at a distance.

THE USE OF THE ELECTROCARDIOGRAPH

It is not intended here to describe fully all the abnormal changes that can beset the electrocardiogram, and only a brief sketch is given of the circumstances in which an electrocardiogram can give valuable information which will cement an insecure diagnosis in diverse abnormal clinical states.

In *congenital heart disease* the electrocardiogram has ceased to be a matter of academic interest, for the application of surgery has demanded a precise diagnosis of the lesion. Thus, the finding of an abnormal electrocardiogram in a patient suspected of *patent ductus arteriosus* should oppose surgical treatment on the grounds that the lesion is complicated by some other anomaly. When the systolic murmur of *pulmonary stenosis* or of *ventricular septal defect* has to be differentiated from an innocent murmur, electro-

cardiographic evidence of right heart hypertrophy points to congenital heart disease as the cause of the murmur. Again, a physiological tracing will by itself exclude a clinical diagnosis of *auricular septal defect*. Left ventricular preponderance in a patient in whom surgery has been proposed for the relief of cyanosis in *Fallot's syndrome* should cause its abandonment because some other lesion is causing the cyanosis, either in part or in entirety.

In the diagnosis of *arrhythmia* the electrocardiogram may prove indispensable and it is often needed to differentiate *auricular fibrillation* from multiple *extrasystoles*, or to interpret a slow irregular pulse as fibrillation or *heart block*. The rapid pulse may also require the help of an electrocardiograph to distinguish *sinus* from *paroxysmal tachycardia*, whilst the treatment of *auricular tachycardia* (auricular flutter) can never be satisfactory without the facilities of the test. In a patient susceptible to paroxysmal tachycardia a tracing taken between the attacks may show a short P-R interval with ventricular complexes resembling those found in bundle branch block (*Wolff-Parkinson-White syndrome*).

Sometimes the diagnosis of *hypertension* may be in doubt when the blood pressure has been lowered by cardiac infarction or, less commonly, by heart failure. In this event an electrocardiographic examination may prove more informative than a radiological one, for it will show a small R wave in the right pectoral lead (CR₁), a tall R in the left posterior axillary lead (CR₇), and R-T depression with a low or inverted T wave in leads I and CR₇.

Massive pulmonary embolism deforms the electrocardiogram in a characteristic way: a most valuable test when the recognition of this catastrophe proves difficult. At the beginning of the illness there may be right bundle branch block which later gives way to the changes of right heart preponderance instanced by a deep S wave in lead I, and inversion of the T wave in leads III, II and CR₁, with a lessening of the S wave in the last lead.

Unfortunately the electrocardiogram does not as yet help materially in the diagnosis of *early rheumatic heart disease*, although it is deformed in the well-developed valvular lesions.

Acute pericarditis elevates the R-T segment and produces a curve with its concavity directed upwards, saddle-like, and dissimilar from the domed curve found in recent cardiac infarction. In *constrictive pericarditis* there is noticeable inversion of the T wave as a rule in most of the limb and chest leads; the number of leads involved depends upon the distribution of the pericardial adhesions which burrow into the myocardium.

A characteristic electrocardiogram is also present in *diphtheria*, *Friedreich's disease*, *myotonia atrophica*, *periodic paralysis*, *Addison's disease*, *myxœdema*, *Simmonds's disease*, and *familial cardiomegaly*, but it is of small importance in some of these conditions, either on account of their rarity or because the diagnosis can be made on grounds other than electrocardiographic.

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the deformed wave should always be tested because the inverted T of cardiac infarction is never wholly corrected by this manœuvre. This simple respiratory test fulfils so important a function in the investigation of cardiac pain, and especially in the search for posterior infarction, that I propose for it the special designation of III(R), signifying that lead III has been recorded during deep inspiration which has depressed the diaphragm. In the third electrocardiographic pattern of cardiac pain the T wave is inverted in leads I and CR₇, telling of *antero-lateral* infarction.

Other abnormalities in the tracing which do not conform to the three types just described, are also met with and indicate coronary disease of undetermined location, but the opinion is held here that as soon as all the irregularities of the electrocardiogram associated with cardiac infarction are known, there is a need to follow a simpler form of diagnosis in terms of *cardiac infarction* and without any reference to its anatomical situation, as the limits of the infarcted area are seldom constant, and especially as its location in no way determines prognosis. Although the electrocardiogram of cardiac infarction is never a normal tracing, the one belonging to *cardiac ischæmia* requires further study; this much may be said already, that the more often electrocardiography is performed in patients with this symptom, the more often will it be found to be abnormal, as in infarction. It is to the investigation of cardiac pain and coronary artery disease that electrocardiographic research is now being most energetically directed and is soon to produce its most beneficial discoveries.

THE ABUSE OF THE ELECTROCARDIOGRAPH

Instruments of precision in good hands can do good work, but in careless hands they have wrought havoc. This truth, directed to the electrocardiograph, has a particularly poignant meaning in that the material it can spoil is human and not inanimate. An uninformed observer with an electrocardiograph can more easily despoil lives than a reckless car driver on a busy highway. On this account it would seem as reasonable to insist on a proficiency test for the electrocardiographist as a driving test for the owner of an automobile. To know how to read an electrocardiogram should be a prerequisite to possessing an electrocardiograph in days when the machine is easily procurable and the demand for its services by a health-conscious laity daily increasing. In keeping with this was the visit of a patient the other day "to see how his T wave was going on". The insistence on the test, however, is a fault more common to doctors than to patients. Examples of this travesty of its use abound, and one such was the demand that the electrocardiograph should accompany the consultant visiting a patient whose activities were said to be retarded and whose ankles had been swollen from heart failure, but in whom a superficial clinical examination made it clear that the former was the result of paralysis agitans and the latter was the outcome of a severe anæmia; a *non-cardiographic* examination showed that the heart was healthy.

THE ELUCIDATION OF CARDIAC PAIN

The electrocardiogram gives greatest help in the diagnosis of cardiac pain: in the elucidation of this symptom the test has no equal and no substitute, and for this reason it should never be omitted in the analysis of the complaint. To ignore it is to court disaster; to use it systematically is to gain help in diagnosis unmatched by any other experience in clinical medicine. Although much is known about the electrocardiogram of cardiac pain there is more to learn about it, and the immediate years ahead are likely to add materially to the appreciation of the part it can play in earlier diagnosis and its expected variation according to the distribution of the myocardial injury which produces it.

First, there is the decision to take on the particular chest leads to record when changes in the limb leads are equivocal; observers differ in their practice, but the choice of C_1 (right pectoral), C_4 (apical), and C_7 (left posterior axillary), is likely to prove the most satisfactory. C_2 might be preferred to C_1 , but nothing will show in the former that is not present in the latter. The greater need in this connexion is to emphasize the importance of recording C_7 , because of the frequency with which this lead shows changes which are not present in C_5 and hardly evident in C_6 .

When it has been decided which station on the chest is most appropriate to receive the exploring electrode it is necessary to choose between the bipolar and unipolar type of electrocardiogram; it is claimed for the second of these methods that it provides an almost neutral polarity for the indifferent electrode, but in practice the lead from the right arm (CR leads) gives a stability to the normal tracing which is greater than that found in any other kind of lead combination so far designed. Certainly those accustomed to work with CR leads need not change to CF or V leads in the belief that they will find in them a superior device for the diagnosis of heart disease, for this belief has been shown to be ill-founded by a comparison of the three methods in healthy subjects and in patients with heart disease.

It is unusual, although not rare, to find deformity in the chest leads from *coronary artery disease*, which is absent in the limb lead cardiogram, but it is common to find a sign portrayed obviously in a chest lead and only indifferently exhibited in the limb leads. For this reason the necessity to record chest lead electrocardiograms in a patient with cardiac pain is evident, and the additional trouble which this procedure entails brings abundant reward from easier and surer diagnosis.

Commonly the electrocardiographic design of *cardiac infarction* conforms to three types. In *anterior* infarction the T wave is inverted in leads I and CR_4 ; should the ventricular septum be involved there is added a deep Q wave in CR_1 . In *posterior* infarction the T wave is inverted in lead III, is often abnormal in lead II, and is usually low or inverted in CR_7 ; the Q wave is prominent in lead III and often in lead II as well. In assessing the significance of T wave inversion in lead III, the effect of deep inspiration on

TRAUMATIC LESIONS OF THE HEART AND GREAT VESSELS

By PAUL H. WOOD, O.B.E., M.D., F.R.C.P.

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DIRECT injury to the heart may be caused by stab or gunshot wounds, and very rarely by diagnostic procedures such as needling the pericardium. The literature on the subject has been well surveyed by King (1941) and by Barber (1944).

GUNSHOT WOUNDS

A bullet or piece of shrapnel may perforate the heart through and through, may lodge in the myocardium or pericardium with or without perforation of one or more chambers, or may graze the surface of the heart without causing death.

In an analysis of 25 instances of war wounds involving the heart, made in conjunction with Nicholson in 1945, the relative incidence of such lesions was as follows:—

Near misses.....	4
Grazes or tangential wounds	4
Through and through perforation	3
Foreign body in pericardium	7
Foreign body in myocardium	7

Of 1,640 consecutive penetrating chest wounds treated at Nicholson's centre, the heart was directly or indirectly injured in 1.7 per cent. The immediate result is hæmopericardium and the rapid development of cardiac tamponade. If a foreign body passes close to the heart or lodges within half an inch of its surface, a transient pericardial serous effusion may develop.

If the patient does not die from cardiac tamponade or hæmorrhage into the pleural cavity, complete recovery may follow, whether a metallic foreign body remains in the heart or not.

Complications.—The chief complication during convalescence is recurrent acute pericarditis: this is nearly always associated with the presence of a foreign body, either in the pericardium or closely connected with it (Wood, 1945). It rarely arises when a bullet is embedded deeply in the myocardium. The attacks tend to be severe, with pain, fever, tachycardia, gross electrocardiographic changes, and the rapid development of a sterile serous effusion which may cause cardiac tamponade. They usually last for about a week. The first attack may occur at any time during convalescence up to about three months after the injury, and may recur several times at intervals of about a month. Of five such cases studied by me in the second world war, all finally recovered, three without interference and two after removal of the foreign body by Nicholson (1945).

A second complication is coronary thrombosis during convalescence.

Another time came a confession from a doctor that the chief purpose of the consultation had been born of a desire to see at work a newer kind of direct writing electrocardiograph.

Coarse body tremors affecting the tracing have sometimes been interpreted as fibrillation and resulted in unnecessary digitalization, whilst the electrocardiographic effects of digitalis therapy have often miscarried opinion, leading to a false diagnosis of cardiac infarction.

A wrong diagnosis, although sometimes inevitable, is always a disappointment, but an unwarranted diagnosis of heart trouble in an erstwhile healthy subject is unpardonable.

It was inversion of the T wave in lead III from a raised diaphragm in abdominal obesity that delegated a navy weighing sixteen stone to lie under his bedclothes for six weeks during a hot summer, and under the added burden of a mistaken diagnosis of cardiac infarction. An inversion of the T wave in CR₄ condemned an active young surgeon to undergo the same penance; he was allowed to become ambulatory after his T wave deformity had been corrected by reversing the electrodes which had been misapplied in the first electrocardiogram that had incriminated his then healthy heart. On another occasion coronary disease had been inferred from the finding of a low voltage curve in the electrocardiogram, but the batteries were shown to be weaker than the heart and were expected to die much earlier than the patient.

The advantages of a properly recorded electrocardiogram need not be extolled, for the test has proved its worth, but the warning bears repetition that the fallacies connected with it should be understood fully, and that its irregularities must be considered at all times alongside the symptomatology and physical signs elicited during a clinical examination of the patient. The electrocardiograph is meant to serve the clinician in his search for signs of an injury to the heart; it will do this unerringly only so long as it is used judiciously and by someone who can read its writing.

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A second complication is coronary thrombosis during convalescence,

when a pericardial foreign body is lodged in contact with a major coronary vessel; but this was observed only once.

Diagnosis.—The possibility of cardiac injury should be considered in all cases of gunshot wounds of the trunk or neck, especially if the missile is judged to have been directed towards the heart, or if its direction is not known for certain. Early diagnosis depends upon recognizing the signs of cardiac tamponade or hæmopericardium. An electrocardiogram may be most helpful by showing the presence or absence of the pericardial T₂ pattern. An intracardiac or pericardial foreign body may readily be detected by means of fluoroscopy, but may easily be overlooked in skiagrams.

Treatment.—It is impossible to say how many lives might be saved by early surgical repair of cardiac wounds. In the second world war the majority of recognized cases survived without such early repair, or at least lived long enough to be evacuated to general hospitals; they were therefore all relatively favourable cases, and the great majority recovered. Relief of cardiac tamponade by paracentesis may be life-saving, both in the early stages or during a later attack of acute pericarditis. Metallic foreign bodies lodged in the pericardium are best removed in view of the danger of recurrent pericarditis; although none of the attacks witnessed proved fatal, the episodes were most alarming. Intracardiac foreign bodies should probably be removed if superficial, and left alone if deep.

Prognosis.—Only one of the 25 patients previously mentioned died; but as already stated these were favourable cases in that they had survived until evacuated to a general hospital. Follow-up studies are incomplete, but the worst case, with three attacks of recurrent pericarditis and a machine gun bullet embedded in the wall of the right ventricle, was alive and well two years after being wounded. On the whole it seems likely that the ultimate fate of these patients is favourable.

STAB WOUNDS OF THE HEART

Direct injury to the heart in civil life is usually due to single or multiple stab wounds, the majority of which penetrate the right ventricle. The clinical, physiological, radiological, and electrocardiographic features of cases which have survived long enough to receive medical aid have been chiefly those of hæmopericardium (Wood, 1937). Death from hæmorrhage into the pleural cavity or from cardiac tamponade may be prevented by timely surgical repair.

Even when patients appear to be holding their own, it is probably wise to evacuate the blood clot and to repair and sterilize the wound as soon as possible; for hæmorrhage may continue or recur, and serious cardiac tamponade develops in most cases. Moreover, if tamponade is left unrelieved too long, acute coronary insufficiency may seriously impair the function of the myocardium, and when it is finally relieved, death may result from acute heart failure. The development of a bulge on the left border of the heart, simulating the appearances of ventricular aneurysm, should not deter the

surgeon, for this is likely to prove no more than a localized pericardial hæmatoma.

EFFECTS OF INDIRECT INJURY

Indirect injury to the heart may be caused by crushes, blows, falls or blast. The effects include sudden death from ventricular fibrillation or standstill, rupture of the aorta, rupture of one or more chambers of the heart, rupture of the aortic or mitral valve, hæmopericardium, myocardial bruising, auricular fibrillation and heart block. Coronary occlusion and subsequent angina pectoris or cardiac infarction may also occur, but their relationship to trauma is less well understood.

SUDDEN DEATH

A heavy blow in the region covering the heart may cause sudden death from ventricular fibrillation or cardiac rupture, both naturally and experimentally in dogs (Bright and Beck, 1935).

There have been numerous instances of sudden death resulting from relatively minor trauma of a kind quite incapable of damaging the heart. The catastrophe is then ascribed to ventricular fibrillation induced by neurogenic shock. Sudden immersion in icy water, extreme fright, or a blow over the heart insufficient to cause material damage may act in this way. Two factors seem important in these instances: a certain diathesis which used to be called *status lymphaticus*, but which is probably more related to suprarenal function; and a ventricle prone to fibrillation, as in elderly subjects, or in those with subclinical coronary artery disease.

This type of death is similar to that which may be caused by a small pulmonary embolism in experiments in dogs, the size of the embolism being quite insufficient to embarrass the circulation, and death being preventable by atropine. The mechanism is probably a vagal reflex. It is possible that ventricular standstill may be responsible, rather than ventricular fibrillation, but experiments favour the latter.

Rupture of the aorta is more likely to occur from a fall, especially if there is congenital hypoplasia as in many cases of coarctation. Hæmorrhage is usually into the pleural cavity or pericardium.

RUPTURE OF THE HEART

Rupture of one or more chambers of the heart following trauma is not always immediate, nor does it always cause sudden death. A myocardial bruise may result in cardiac aneurysm or delayed rupture, usually during the second week, as described by Bright and Beck (1935).

These authors collected from the literature over 150 cases of traumatic rupture of the heart, and found the incidence of the various chambers involved to be as follows:—

Left ventricle	37
Right ventricle	31
Left auricle	30
Right auricle	36
More than one chamber	13
Interventricular septum	11
Interauricular septum	1

It will be appreciated that this distribution is very different from that seen with spontaneous rupture secondary to cardiac infarction, when the left ventricle is nearly always responsible.

The latent interval was also studied by Warburg (1938). It occurred in 15 out of 51 cases proved at autopsy. A small tear may behave similarly to a direct penetrating wound that causes delayed death from hæmopericardium, usually within a few days. A bruise may rupture at any time within six weeks (Barber, 1938), or occasionally after a longer interval. Cardiac aneurysm resulting from a bruise may rupture years afterwards (Joachim and Mays, 1927).

During the quiescent phase the patient may seem relatively well, any discomfort being attributed to the bruise on the chest, and he may continue his normal activities, including sport (Priest, 1939). In other cases symptoms may result from hæmopericardium or from any of the other effects to be described later.

Diagnosis.—If the patient is seen alive after cardiac rupture, the signs and symptoms are those of hæmorrhage into the pericardium or pleural cavity. The combination of collapse, rapid thready pulse, and a high jugular venous pressure from cardiac tamponade, is very suggestive if discovered within a month of injury. There may be no evidence of external damage to the chest wall, and the history of the accident may not be mentioned, for it may not appear to be connected with the illness. If the possibility of previous trauma is considered, the diagnosis is usually obvious.

Treatment.—Immediate surgical repair is the only hope of saving life.

HÆMOPERICARDIUM

Symptoms and signs of pericarditis, with or without hæmopericardium, are relatively common after indirect cardiac trauma, particularly perhaps after blast injury. They provide useful evidence of cardiac damage, but do not necessarily indicate its nature. Surgical interference is only warranted if there is tamponade, which usually signifies cardiac rupture or serious coronary hæmorrhage. Many cases have recovered spontaneously (Smith and McKeown, 1939).

MYOCARDIAL BRUISING

Crushing of the chest, direct blows over the heart, and blast, may all cause myocardial contusion, the clinical picture resembling that of myocardial infarction, including the characteristic electrocardiographic changes, or heart failure without pain (Barber, 1944; Barber and Osborn, 1941).

It is of considerable interest and medico-legal importance that following a direct blow in the præcordial region, electrocardiographic changes may occur which are indistinguishable from posterior myocardial infarction (Anderson, 1940). Although it is possible that this represents remote contusion, it is perhaps more likely that an anterior lesion may occlude the right

coronary artery. This kind of effect will be considered more fully later. The chief danger of myocardial contusion is delayed rupture, as previously described.

Treatment consists of rest in bed for six weeks, semi-starvation, a low sodium intake, mersalyl if necessary, sedatives, and avoidance of digitalis.

RUPTURED AORTIC CUSP

Indirect trauma sometimes ruptures an aortic cusp. There may or may not be underlying aortic valve disease, congenital or acquired. The lesion results in the abrupt development of aortic incompetence, which throws a heavy burden upon an unprepared left ventricle, so that failure of that chamber is likely to ensue.

The *diagnosis* is suggested by the sudden onset of orthopnoea, paroxysmal cardiac dyspnoea, or pulmonary oedema, following a serious fall or other violent accident, and is confirmed by the discovery of a loud, harsh, sometimes musical, aortic diastolic murmur, often accompanied by a thrill, especially if the valve was known to have been normal previously.

The *prognosis* may be good if the patient survives the immediate insult, but death from heart failure within six weeks is a grave risk (Barber, 1938, 1944).

Treatment consists of six weeks' rest in bed in order to allow time for adequate compensation, and may have to be directed towards combating left ventricular failure. It must be understood that a degree of aortic incompetence which would be well tolerated and consistent with years of active life if it had developed slowly, may cause death from acute heart failure when it occurs abruptly; just as acute hypertension may cause left ventricular failure and pulmonary oedema, whereas much higher pressures may be tolerated when developing slowly in benign hypertension.

TRAUMATIC MITRAL INCOMPETENCE

A severe fall, or a sudden blow over the heart, or other violent accident may occasionally rupture chordae tendineae or tear one of the mitral cusps, particularly if already diseased. The lesion is rare, but there are many well-authenticated instances (Barber and Osborn, 1937). A clinical diagnosis may be made on the history, if it is known that no murmur was present before the accident, if a loud harsh mitral systolic murmur is heard when the heart is first examined after the accident, if there is no evidence of previous rheumatic valve disease, and if confirmatory signs of organic mitral incompetence develop, e.g. mitral systolic thrill, left ventricular enlargement, and systolic expansion of the left auricle.

A number of cases have died from congestive heart failure within a few hours or weeks of the accident, and others have developed mitral stenosis later (Barber, 1938). On the other hand, the accidental discovery of

symptomless mitral incompetence attributable to trauma need cause little alarm, such cases behaving like rheumatic mitral incompetence with a healthy myocardium.

HEART BLOCK

There have been a number of instances of asphyxia in which hæmorrhage has taken place around the bundle of His, with resulting heart block. I have seen several cases at autopsy, and a good example was observed during the 1940-41 London air raids:—

A woman of about thirty-five, known to have been in previous good health, was rescued in a partly asphyxiated condition from beneath a lot of debris. Examination shortly afterwards revealed not only complete heart block, but also gross signs of hemi-Parkinsonism, presumably due to hæmorrhage into the bundle of His and into the substantia nigra. She declared that she had received no severe blow on her chest, nor significant crush, but had been partly asphyxiated by dust for about one hour.

Heart block may also result from a blow over the heart or from a fall on the chest (Coffen, 1930; Warburg, 1938), and has been so produced experimentally in dogs (Kissane, 1937). Hæmorrhage into the conducting system is presumably responsible. The lesion may be transient or permanent, the prognosis depending upon the presence or absence of Stokes-Adams' fits, and upon the rate of the idioventricular pace-maker; but on the whole it is fairly good, provided there is no more serious injury, the heart muscle being sound.

AURICULAR FIBRILLATION (OR FLUTTER)

A number of instances of auricular fibrillation have been caused or precipitated by blows (Kahn and Kahn, 1929), particularly in the elderly (Barber, 1938). Bramwell (1934) records a case in which auricular fibrillation was probably initiated by a head injury, and Hay and Jones (1927) describe one due to electric shock. Not only head injury, but also meningitis, Ménière's syndrome, and probably other intracranial events may excite this rhythm change.

CARDIAC INFARCTION AND ANGINA PECTORIS

As already described, myocardial contusion may give rise to clinical and electrocardiographic features similar to those of myocardial infarction, and may also result in cardiac rupture or aneurysm. But there appears to be a closer relationship between trauma and ischæmic effects: thus an anterior injury to the chest may cause a posterior left ventricular lesion clinically indistinguishable from a cardiac infarct, and classical angina pectoris may develop for the first time immediately after trauma (Campbell, 1939). Moreover, the subsequent course of these cases may be that of idiopathic ischæmic heart disease. It is possible that blows, crush injuries, and blast may injure the anterior coronary vessels, either by causing sub-intimal

hæmorrhage in an atherosclerotic artery, or more directly, and thus cause acute coronary occlusion or secondary thrombosis. After such an event subsequent angina pectoris would be readily understood. Great care must, however, be taken in diagnosing traumatic angina, for many persistent chest pains following injury represent a compensation neurosis.

Treatment consists of three to six weeks' rest in bed, followed by one to three months' convalescence, to allow time for the development of adequate collateral vascularization. The prognosis depends upon the degree of underlying coronary disease, as well as upon the amount of damage inflicted. On the whole it is not dissimilar to that in ischæmic heart disease in general.

MEDICO-LEGAL ASPECTS

Employees are entitled to compensation if it can be shown that trauma has initiated or aggravated a cardiovascular disability. Even a case of syphilitic aneurysm that ruptures during the course of work receives compensation. Patients with established heart disease may deteriorate after an accident, and this aggravation is equally compensated. The benefit of doubt is always given to the patient, and in a court of Law or tribunal it is difficult to convince a judge or president that trauma has not adversely affected the cardiovascular system. Yet a firm stand must be taken over the development of cardiac neurosis. Left inframammary pain is especially liable to become persistent and intractable if linked to the idea of compensation, and the physician must be prepared to make a categorical statement to the effect that this is not organic and is not due to the accident: that its origin lies in the mind and in the emotions, and that its growth runs parallel with the conscious or subconscious desire for gain.

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THE SURGERY OF THE HEART

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THE surgery of the heart may be said to have begun in the closing years of the 19th century when Rehn first successfully sutured a wound of the heart. This brilliant operation, which demonstrated that the heart was amenable to surgical interference, suggested possible great advances in the surgical treatment of other forms of heart disease. The time, however, was not ripe, for although many successful operations for wounds were recorded, progress in other conditions was slow. Nearly half a century was to elapse before the rapid development envisaged earlier began to appear. In the intervening years a few new operations were introduced but the surgery of the heart showed few signs of being firmly established like the surgery of other parts of the body.

These intervening years, however, brought many advances which have made it possible to develop cardiac surgery more as a definite science than as a series of rather halting operations. They include the advance of surgical technique in general, the avoidance of shock, the routine use and ready availability of intravenous infusion and of blood transfusion, chemotherapy, and great advances in anaesthesia, especially anaesthesia for operations on the chest. During the last fifteen years the surgery of the open thorax has become firmly established and the development of cardiac surgery then became inevitable.

As in other difficult fields of surgery there is no place for the lone operator in heart surgery. He must work as one of a team which will include a physician cardiologist, radiologist, physiologist and biochemist, and expert anaesthetists and assistants. Without such team-work no really good work, and certainly no advance, is possible.

DIAGNOSTIC METHODS

When an operation upon the heart is proposed it is essential that the diagnosis should be as accurate and as complete as possible. In the old days when little active or radical treatment was employed there was less need for precision. The urgency of a complete diagnosis has meant the development of many new methods of investigation in addition to electrocardiography. Besides various physiological tests much valuable information is being obtained from angiocardiology and from cardiac catheterization.

Angiocardiography is done by injecting a radio-opaque substance with a high (70 per cent.) iodine content into an arm vein very rapidly (less than 2 seconds) and then taking a rapid series of radiographs which will show the various chambers of the heart and the great vessels rendered opaque.

In *cardiac catheterization* a fine catheter is introduced through a vein into

the venæ cavæ, then into the right auricle, the right ventricle, and finally into the main pulmonary artery and its branches. By recording the pressures in the different chambers and by studying the oxygen content of the blood, a great deal of valuable information can be obtained. It is, for instance, possible to diagnose various septal defects with certainty, and in some cases the catheter may even be shown to pass from the right to the left side of the heart through such defects. Cardiac catheterization and angio-cardiography are essentially complementary in the information they afford.

THE SCOPE OF CARDIAC SURGERY

The surgery of the heart was founded on the surgery of trauma, and perhaps one of the most spectacular developments, especially during the late war, is the successful removal of missiles actually from within the chambers of the heart. Many have been successfully removed from the wall of the heart and from the pericardium.

Pericarditis.—Acute septic pericarditis may require relief by surgical drainage. Although penicillin and the sulphonamides have cured many cases without operation they have not done away with the need for operation; indeed their use often enables the patient to survive the more desperate infective phases of the illness and to reach the stage when surgery can afford relief from the mechanical and toxic effects of an accumulation of purulent fluid, often with fibrin clots that prevent successful aspiration through a needle. Cardiac tamponade is the condition that results from a high pressure within the pericardium preventing venous filling of the heart and hence diminishing the cardiac output. Aspiration may relieve this for a time but usually open drainage is required if life is to be saved.

In certain forms of chronic pericarditis the fibrous tissue contracts relentlessly and holds the heart disabled like a hand in a tight glove. In this condition of "constrictive pericarditis" the diastolic filling of the ventricles is impeded, and thus the cardiac output falls and venous obstruction and congestion ensue. It can be dramatically relieved by excision of the thickened pericardium. Many cases of this type (Pick's disease) remain unrecognized and go to their deaths diagnosed as "ascites", "congestive heart failure", and the like.

Cardiac ischæmia and angina pectoris.—It has been stated that cardiac ischæmia from coronary arterial disease is responsible for more deaths after the age of forty than any other condition. Angina pectoris is frequently an accompaniment, and although it is often a prelude to an early death, or may be relieved by simple means, it not infrequently presents as a symptom of such severity and persistence that it calls for relief by any possible means.

The logical thing is to try to improve the blood supply to the heart, thus relieving the primary condition of ischæmia and also the anginal pain which is often the result of the ischæmia. Various operations (e.g. cardio-omentopexy) have been devised and practised to try and augment the flow

of blood to the heart, but for the most part their mortality has been too high and the results sufficiently uncertain to prevent their wide and confident acceptance. A less severe method of affording relief of anginal pain consists in excising the upper thoracic sympathetic ganglia and nerves. This can give dramatically successful results, and although it might be argued that a useful warning symptom is lost, this is not so. A mild sensation of discomfort may remain but the crippling pain is relieved, and activity is greatly increased.

CONGENITAL HEART DISEASE

A few years ago congenital heart disease was a hopeless condition for which no relief could be offered. The advances in surgery are truly astonishing and often cure, or help to cure, many sufferers.

Patent ductus arteriosus.—The first big step forward was made when ligation of the patent ductus arteriosus was successfully performed by Gross in 1939. Many cases of patent ductus are found in children in the course of routine medical examination, and it is often difficult to advise with confidence whether these cases should be operated upon or not. In this connexion it should be remembered that in this condition there is an arterio-venous leak that throws much extra work upon the heart, leading ultimately to its enlargement and failure. In addition, about 40 per cent. of patients die from infective endarteritis of the pulmonary artery, a condition which is liable to supervene after the onset of puberty. This infective process is often difficult to diagnose and its significance is often overlooked; the mortality is high. Few cases of patent ductus arteriosus are seen over the age of twenty-five years; although this might be due to spontaneous cure it is more likely to be due to the fact that death has been the weeding process. In expert hands the mortality of operation is low, less than 5 per cent.; when complications, particularly infection, have appeared, the risk rises. Successful ligation restores the heart condition to normal; the patient is completely cured.

Coarctation of the aorta.—This condition, previously untreatable, is now curable owing to the work of Crafoord, who showed in 1944 that it could be treated successfully by resection of the strictured portion of the aorta and restoration of continuity by end-to-end anastomosis. Many cases have now been operated upon, and in skilled hands the mortality is less than 10 per cent. Much of what has been said about patent ductus arteriosus applies to this condition also. When found accidentally and causing no symptoms it may be difficult to advise an operation of such magnitude. It is, in general, a killing disease as a result of the hypertension that it causes in the head and upper extremities. The patients die from cerebral hæmorrhage, cardiac failure, or rupture of the aorta. Once thought of, the diagnosis can be very easy; the finding of hypertension in a young adult should lead to examination of the femoral pulses (which are absent or greatly diminished) and a

search for collateral arteries over the chest wall. Skiagrams of the chest show characteristic notching of the ribs caused by the dilated, tortuous, intercostal vessels. As yet, no late results of operation are available, but with restoration of a normal lumen to the aorta in a young patient the prognosis after successful operation should be good.

Cyanotic heart disease.—The group of patients with cyanosis from congenital heart disease (blue babies) formed one of the most hopeless of all conditions. The outlook has now been greatly changed owing to the brilliant work of Blalock and Taussig. Few of these patients ordinarily reach puberty and it is rare for any to survive beyond the middle twenties. They remain a constant burden and distress to their parents, and death is often a merciful release from a life of suffering and painfully restricted activity and invalidism. This cyanotic group includes a number of types of congenital heart disease, most of which are complex. It is in this group in particular that the fullest and most precise diagnosis is necessary and in which the modern methods of investigation find their greatest value.

Blalock and Taussig pointed out that, although the cyanosis is partly caused by various intracardiac shunts causing mixing of arterial and venous blood, the main cause of the disability, and a great cause of the cyanosis, is the fact that an inadequate supply of blood goes to the lungs. They therefore proposed to correct this by anastomosing a systemic artery, such as the subclavian or innominate, to the right or left pulmonary artery. The operation is a delicate, complex and difficult one and is not suitable for the casual operator. A good organization and good team work are essential for good results, but given these the results have been brilliantly successful. The immediate mortality is rather high, being between 10 and 15 per cent. even in skilled hands, but in about 75 per cent. of cases the final result is excellent. The polycythæmia goes, the colour becomes normal, or a faint cyanotic tinge may persist after exercise; the exercise tolerance may change from almost *nil* to almost normal. Children who could walk only a few yards, and that with distress and cyanosis, are able to run and play normally and to walk many miles. Arrest of physical development is common before operation. The best time for operation is between the ages of three and ten years. Below the age of three the risks are greater and the vessels are so small that the stoma may not be large enough as the patient gets older. Patients in the late teens and early twenties are also bad operative risks.

Potts of Chicago introduced an important modification of the Blalock procedure in which the anastomosis is performed directly between a pulmonary artery and the aorta itself, instead of one of its branches. This is made possible by an ingenious clamp, designed by Potts and his colleagues, which occludes part of the lumen of the aorta so that it can be used for the anastomosis while the circulation to the lower part of the body is maintained through the unoccluded portion of the lumen. Potts's operation is of especial value in very young children in whom the subclavian artery is too

of blood to the heart, but for the most part their mortality has been too high and the results sufficiently uncertain to prevent their wide and confident acceptance. A less severe method of affording relief of anginal pain consists in excising the upper thoracic sympathetic ganglia and nerves. This can give dramatically successful results, and although it might be argued that a useful warning symptom is lost, this is not so. A mild sensation of discomfort may remain but the crippling pain is relieved, and activity is greatly increased.

CONGENITAL HEART DISEASE

A few years ago congenital heart disease was a hopeless condition for which no relief could be offered. The advances in surgery are truly astonishing and often cure, or help to cure, many sufferers.

Patent ductus arteriosus.—The first big step forward was made when ligation of the patent ductus arteriosus was successfully performed by Gross in 1939. Many cases of patent ductus are found in children in the course of routine medical examination, and it is often difficult to advise with confidence whether these cases should be operated upon or not. In this connexion it should be remembered that in this condition there is an arterio-venous leak that throws much extra work upon the heart, leading ultimately to its enlargement and failure. In addition, about 40 per cent. of patients die from infective endarteritis of the pulmonary artery, a condition which is liable to supervene after the onset of puberty. This infective process is often difficult to diagnose and its significance is often overlooked; the mortality is high. Few cases of patent ductus arteriosus are seen over the age of twenty-five years; although this might be due to spontaneous cure it is more likely to be due to the fact that death has been the weeding process. In expert hands the mortality of operation is low, less than 5 per cent.; when complications, particularly infection, have appeared, the risk rises. Successful ligation restores the heart condition to normal; the patient is completely cured.

Coarctation of the aorta.—This condition, previously untreatable, is now curable owing to the work of Crafoord, who showed in 1944 that it could be treated successfully by resection of the strictured portion of the aorta and restoration of continuity by end-to-end anastomosis. Many cases have now been operated upon, and in skilled hands the mortality is less than 10 per cent. Much of what has been said about patent ductus arteriosus applies to this condition also. When found accidentally and causing no symptoms it may be difficult to advise an operation of such magnitude. It is, in general, a killing disease as a result of the hypertension that it causes in the head and upper extremities. The patients die from cerebral hæmorrhage, cardiac failure, or rupture of the aorta. Once thought of, the diagnosis can be very easy; the finding of hypertension in a young adult should lead to examination of the femoral pulses (which are absent or greatly diminished) and a

THE RIDDLE OF RHEUMATOID ARTHRITIS

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MANY important and intriguing problems in the field of medicine are undergoing intensive study and are awaiting solution. Great activity in the form of both individual and cooperative investigation is already being applied to some of these problems, such as cancer, heart disease, and allergy. One of the most important medical problems which has heretofore been largely neglected is that of rheumatoid arthritis. It is estimated that one-fourth to one-third of the victims of chronic rheumatic diseases have rheumatoid arthritis. It is the rheumatic disease which most frequently leads to lamming and crippling and is often the cause of deformities resulting in complete disability which may persist for decades. Because conventional medical and surgical care is so often unsatisfactory, the victim is inclined to succumb to the advice of well-meaning friends and to submit to the ministrations of the quack, the faith healer, the herb doctor and the diet faddist. The history of the disease reveals that the widest possible variety of remedies has been recommended. Many suggestions in their turn have gained considerable popularity. Occasionally treatments have attained almost universal acclaim for varying periods of time, only to lapse into unpopularity and finally to fall into disuse. Consideration of the problem of rheumatoid arthritis indicates that several factors combine to make such a situation almost inevitable.

THE MULTIPLICITY OF TREATMENTS

A review of the treatments currently and formerly used for rheumatoid arthritis can be instructive. These include liniments, salves, and Epsom salt soaks for local application, analgesic drugs such as salicylates, cinchophen, iodoxy benzoate, opiates and their substitutes, potassium iodide and bromides. Biological agents include streptococcal, staphylococcal and mixed vaccines, supposed to be either specific or non-specific; autogenous or stock vaccines designed for intravenous, intradermal or subcutaneous injections. These are administered in one instance in an effort to immunize the patient, in another instance to desensitize the patient, or in a third instance to produce a non-specific protein shock reaction with or without fever. Many types of protein and protein derivatives have been employed to induce fever. Such measures as natural hot springs, mineral waters and the Zander apparatus in gymnasiums were forerunners of modern physical and fever therapy.

small to provide an effective stoma. It is also valuable in older patients when the subclavian artery is too short or too narrow to be used. Blalock has used the carotid or innominate arteries in such cases, but the mortality is very high (33 per cent.) and the risk of hemiplegia is great. It is doubtful if it is ever justifiable to use the carotid or innominate vessels when the aorta provides a ready means of avoiding the dangers of severe or fatal cerebral damage.

The Blalock-Taussig operation provides a relief from the present dangers and disability of cyanosis and anoxæmia; it does not relieve the pulmonary stenosis. Indeed, by creating an artificial *ductus arteriosus* it actually introduces a new element of abnormality into the heart condition, and as a result it is probable that in later years death will occur from congestive heart failure or infective endarteritis. As Blalock has truly said: "there is no justification for letting a patient die of anoxæmia now just because he may get a complication in later years". This difficulty does, however, suggest the feasibility of relieving the condition by lessening or correcting the pulmonary stenosis. In many of the cases the stenosis lies below the pulmonary valves within the walls of the right ventricle; it is obviously very difficult to treat this state of affairs. In a proportion of cases the stenosis affects the pulmonary valves and it has recently been shown that this is capable of relief by direct operation upon the valves. Results have been obtained as good as those that follow a successful Blalock operation. Much work remains to be done before a final assessment can be made of this procedure.

VALVULAR STENOSIS

In addition to the relief of congenital pulmonary stenosis by valvulotomy, there is the problem of the relief of post-rheumatic valvular stenosis (in particular, of course, mitral stenosis) by surgical operation. Attempts to solve the problem were made a quarter of a century ago and met with such scant success that they were virtually abandoned. The time is now fully ripe for renewed attack upon this problem, for it is a big one, the solution of which will offer relief to the large numbers of sufferers from mitral stenosis who are now disabled and marked for an early death. It is at present only possible to say that successful operations have been done in this country, and that the immediate future will undoubtedly show great and gratifying advances in this most difficult field.

THE FUTURE

The advances of the last decade in the surgery of the heart have been so great, many of them so unforeseen, that he would be a courageous man who would predict what the next decade will bring. It is certain, however, that it will see the firm establishment of most of the current surgical procedures outlined here and doubtless many other advances as yet scarcely thought of.

many months, and joint involvement may be so slowly progressive that the true nature of the disease is not recognized for months or for several years. Different patients may or may not exhibit involvement of one or of all joints. The joints may be greatly enlarged with periarticular thickening, and they may be distended by intra-articular fluid. The typical spindle-shaped or fusiform finger may or may not be present. X-rays may show marked osteoporosis, decreased joint space denoting cartilage destruction, and erosion and distortion of the joint surfaces. The hands and feet may exhibit severe degrees of circulatory disturbance with cyanosis or pallor, extreme perspiration and coldness of the skin.

Muscle weakness, particularly in the vicinity of involved joints, may be extreme and muscle atrophy severe. This may occur suddenly or it may be unnoticed. Muscle soreness and stiffness are characteristic of rheumatoid arthritis. These symptoms vary tremendously in degree from patient to patient. More confusing, however, is the fact that they vary tremendously from hour to hour, day to day, and season to season in the same patient, and they are influenced by changes in the weather. Limitation of joint motility may result from deformity of the joint surface causing bony block. It may be caused by shortening of the joint capsule and muscle tendons, or shortening of the muscles due to spasm. Furthermore, rheumatoid arthritis is characterized by remissions with regression of all symptoms, sometimes lasting for several years, only to be followed later by reactivation of the disease. No chronic disease exhibits a wider variety of manifestations than does rheumatoid arthritis.

DIAGNOSTIC DIFFICULTIES

The discussion so far has been confined to rheumatoid arthritis. A large number of other diseases at different stages of their development are mistakenly diagnosed and treated as rheumatoid arthritis. These include widespread degenerative arthritis, so-called menopausal arthritis, fibrositis, myositis, neuritis, sciatica, herniation of the nucleus pulposus, peritendonitis, periartthritis of the shoulder, spondylitis, periarteritis nodosa, dermatomyositis, and palindromic rheumatism. There are also causalgia, erythromelalgia, acroparæsthesia, angioneurotic œdema and Raynaud's disease. Thus it can be seen that many features of the disease serve to complicate the problems of rheumatoid arthritis. Since no etiological factor has been clearly recognized, specific therapy designed to eradicate the cause of the disease is not available.

THE THERAPEUTIC TANGLE

Treatment is entirely symptomatic, although some people feel that gold therapy may be specific. Many treatments aimed at relieving symptoms rather than treating arthritis are of recognized success. They include aspirin

The prevention and correction of deformities require the use of splints, casts, braces, traction and manipulation, sometimes under anæsthesia. Changes of climate with visits to the seashore, the desert, the mountains and the subtropics are thought to be beneficial. Blood transfusions, pregnancy, and jaundice occasionally produce remissions. Physicians have used injections of colloidal sulphur and now they have copper and gold. Of diets there is no end, including low carbohydrate, low protein, high protein, low purine; 18-day diets confined exclusively to fruit juices; diets confined exclusively to milk; high calorie diets for the undernourished, and low calorie diets for the obese. The vitamins cannot be ignored. Their use has included treatments with vitamin A, various components singly or in combination of vitamin B, vitamin C, massive doses of vitamin D, vitamin E, and unknown combinations of vitamins, such as crude liver extract, brewer's yeast, rice polishings and wheat germ oil. There are bee sting, cobra venom, prostigmin, and the Bogomoletz serum. Of the eclectic treatments which have never received scientific approval may be mentioned the wearing of a copper bracelet, the wrapping of the affected joint in the skin of a black cat, the sprinkling of powdered sulphur in the shoes, and the habit of carrying a horsechestnut or a potato in the trouser pocket!

Some of the treatments listed above are in almost universal use and they have a beneficial effect in certain circumstances; some are effective only against a single symptom. Many of the above measures seem to be completely useless when the criteria of their effectiveness is examined objectively, despite the fact that they are still being employed. Many of the treatments mentioned have been abandoned. The nature of rheumatoid arthritis is such as to make confusion about therapy very likely. Since there is no clear concept of the etiology of the disease, therapeutic ineffectiveness is almost guaranteed.

THE VARIEGATED SYMPTOMATOLOGY

Rheumatoid arthritis seems to have afflicted men since the beginning of civilization. It occurs in all corners of the world and affects all races, ages and sexes. A wide variety of prodromal or precipitating factors has been described. These include the common cold, tonsillitis, streptococcal sore throat, peritonsillar abscess, acute and chronic sinusitis, pneumonia and its complications, typhoid fever, cholera, ulcerative colitis, cystitis, pyelitis and urethritis of gonorrhœa. Debilitating factors which have been implicated include overwork, nervous strain, emotional crises, exposure to cold and dampness, hæmorrhage, pregnancy, lactation, the menarche and the menopause. The onset of rheumatoid arthritis may be acute and febrile with marked constitutional symptoms and prompt involvement of practically all joints, and the disease may progress without intermission until complete and apparently hopeless invalidism and disability are produced within one year. Conversely, the onset may be so mild as to be hardly noticeable for

Although there is no indication at present as to its true nature, there is no reason to doubt that the cause of rheumatoid arthritis is discoverable. The problem must be attacked by many groups of investigators probing at the mystery from different angles as well as by individual enthusiasts working alone. The necessary knowledge leading to a more complete understanding of rheumatoid arthritis can be gradually accumulated if sufficient attention is devoted to it. Some of it will come as a stroke of genius by the recognition of an insignificant or obscure hint which may be observed in a collateral field. Much of the information necessary for a clear understanding of the disease will probably have to be built up by the plodding pursuit of detailed, orderly and well-planned long-range programmes by teams of diligent and determined investigators.

CONCLUSION

I have long been disturbed by the chance remark I heard many years ago by a friend. This friend had recently purchased an 1828 edition of the *Encyclopædia Britannica* and read about malaria. The descriptions he found of the symptoms, the clinical course, the prognosis, the treatment and the pathological findings were quite satisfactory even in the light of modern knowledge. The comments about the cause, the spread and the prevention of malaria were bizarre, fantastic and full of contradictions. They were bizarre, fantastic and full of contradictions until he remembered that malaria was now known to be spread by mosquitoes. On considering the influence of the mosquito many of the bizarre, fantastic and contradictory statements became understandable. They seemed to fit together into a logical and practical plan which was sensible and credible. It did, however, require knowledge of the mosquito to reach this conclusion. My friend said further that he thought it likely that all the factual knowledge necessary for an explanation of rheumatism and arthritis had been available for years. Science had only failed so far to recognize the proper "mosquito". When the "mosquito" is finally discovered, many of the diverse precipitating factors, the different local and constitutional symptoms, the apparently unrelated forms of treatment of rheumatoid arthritis will fit into a logical and related pattern and a specific and effective remedy will be developed. Scientists may then look back and wonder why it took so long to solve the riddle and to see a truth which proved to be so simple and so obvious.

for pain and stiffness, and physical therapy for pain, stiffness and for deformities. Vitamin B complex helps lassitude and iron relieves anæmia.

In testing the effectiveness of a new therapy, a hypothetical series of patients with rheumatoid arthritis is likely to include young and early cases, old and chronic cases, cases which are active and those which are quiescent, severely disabled individuals, and a few patients in whom the diagnosis is questionable. Even if the series be limited to cases of recent onset, the clinical picture in one patient may be dominated by pain, in another by stiffness, in a third by joint swelling, and in a fourth by marked debility. No one treatment so far has been found to be effective against all these symptoms. Because of the wide variation in the clinical symptoms a controlled series, properly balanced, is extremely difficult to develop in rheumatoid arthritis.

No readily recognizable fundamental lesion of rheumatoid arthritis has been recognized which can be used as a guide to treatment. Curious collections of lymphocytes and plasma cells usually grouped about capillaries have been discovered in synovial membranes, periarticular tissues, muscles and nerves of patients with rheumatoid arthritis. They are demonstrable only in histological sections of tissue removed by biopsy or at autopsy. They have not been observed to disappear under treatment or after remission of the disease. They are therefore of no use as a guide to therapy. Nor is any other reliable therapeutic index available. The condition relative to rheumatoid arthritis is much different to that in many other diseases. In pneumonia the temperature falls with penicillin; in diabetes the blood sugar falls with insulin. In pernicious anæmia a reticulocyte response is seen after liver therapy. In rheumatoid arthritis the doctor hardly knows what to hope for when he starts his treatment.

Speaking symbolically, the patient with rheumatoid arthritis might be compared with a house that is on fire. In the beginning and for a short time there may be doubt as to whether or not there actually is a fire. Within a reasonable time a very brisk fire is apparent. The fire department is called, water and chemicals are poured on to the blaze, and certain smouldering areas are literally chopped out and removed from the rest of the building. Finally, the fire is completely extinguished and the ashes become cold. At this stage the fire department can be of no help. The carpenter, painter, and interior decorator are the only ones who can help. So it seems with rheumatoid arthritis: sometimes the fire department is needed; sometimes it takes a carpenter, or painter or an interior decorator.

When the exact cause of rheumatoid arthritis is discovered, an effective specific therapy can probably be developed. It is hoped that one treatment then will relieve many of the symptoms, just as penicillin or heavy metal therapy cures the widely different syphilitic lesions of chancre, mucous patches, skin manifestations and vascular involvement, and as penicillin controls pneumococcal pneumonia as well as pneumococcal meningitis, endocarditis, pericarditis, arthritis and empyema.

brought into a place where it has regularly undergone painful manipulations it shows no anticipation of them until they start, and its crying ceases as it returns to its mother's arms. It is very different with the child of a year or more, who suffers acutely in anticipation and remembers long. The moral is obvious. I am aware that this teaching goes counter to that of some schools of psychology, who maintain that the earlier an impression occurs the stronger is its effect, but to me the two-year old child with a corrected talipes dashing happily and confidently into the consulting room outweighs a good deal of Viennese dogma. The pain sense is also surprisingly ill-developed in tiny babies. In my young days I worked in a famous orthopædic centre where a new-born baby with talipes was always brought to the surgeon accompanied by a tray of tenotomy knives. The tendo Achillis was cut then and there while the mother held the baby. The babies often seemed quite unaffected by the operation, even if the same could not be said for the mothers.

Parents are often worried about the effect that the wearing of splints may have upon a child's mentality. Under two or three years of age they appear to me to be quite unaffected by any consciousness of inferiority at having to wear them. It is far different if they have to go to school with any disfigurement or disability that will serve to arouse the jeers of their little playmates. At the age of five, when schooling usually begins in this country, the child is sensitive enough for the first impact of human cruelty to cause great suffering and damage to his character.

The softness and malleability of the tissues.—This point would seem too obvious to labour, were it not so often ignored. The difference in the resistance of a talipes foot in the newborn from that of a similar one even six months older is most marked.

CONSIDERATIONS INDICATING DELAY IN INTERVENTION

The possibility of spontaneous correction of the deformity.—In many cases in which this reason for delay is put forward the advice is due to confusion between a true and intractable deformity and a much less serious departure from the average appearance which resembles it. The mistaking of an inversion spasm for true talipes, of a retractile testicle for a true mal-descent, or of a napkin walk for bandy-leg, are common instances of this.

Increase in the strength to withstand severe operations.—This is an obvious consideration, although with modern improvements in anæsthesia, one of less importance than it was.

Difficulty of operating on minute and flimsy tissues.—This reason for delay, when it is possible, needs no emphasizing to those who contrast the toughness of many structures of the adult body with their diaphanous and almost impalpable texture in the young. The same qualities that make for ease of manipulation make for difficulty of suture and dissection.

The development of cooperation with age.—When the carrying out of exercises, for example, is a necessary part of the treatment, this must be

THE TIME FACTOR IN THE TREATMENT OF CONGENITAL ABNORMALITIES

By DENIS BROWNE, F.R.C.S.

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THE best age at which to begin to treat congenital abnormalities is a most important question, but one on which definite guidance is difficult to find in standard textbooks. The resultant vagueness is responsible for a good many indifferent results, much unnecessary suffering, and not a few downright tragedies.

In this article an attempt is made to determine the optimum time for interference by stating the factors that make for early intervention, and those which make for delay, and then balancing them against each other to produce a result. In addition, it is of interest to record the practice of this country at the present time, the changes which have occurred in it during my experience, and the improvements that may be hoped for in the future. It is obvious that at present it is rare for a new-born infant to receive anything but the most casual inspection; a curious contrast to the systematic overhaul which a car or a horse would receive from those who have the care of them.

CONSIDERATIONS INDICATING EARLY INTERVENTION

The power of healing and adaptation in the very young.—A well-known instance of this is the way in which a birth fracture of a long bone heals rapidly with an immense outgrowth of callus, and spontaneously corrects displacements and overlapping, which occurring in later life would mean permanent severe deformity.

The avoidance of bad habits.—Many parts of the human body subject to deformities do not come into active use until some time after birth. If they are made capable of normal action during this latent period, the child will not learn to use them wrongly. But should this not be done, a faulty mental picture is formed of the function concerned, and to this picture the child adheres with the utmost obstinacy. A faulty start to the playing of a game is extremely difficult to eradicate; in the same way, when a child stands for the first time upon an abnormally held foot, a surgical disaster has occurred.

The stimulation of development by use.—Much of the literature upon deformities does not pay enough attention to the development of function as opposed to the correction of structure. The heel of a talipes foot, for instance, will not grow to normal size and shape whatever position the foot is placed in, unless a free range of movement at the ankle and strong muscles to take advantage of it is supplied at a very early age.

Avoidance of mental damage to the child.—For all practical purposes the baby in the first few months of life has no memory and no imagination;

brought into a place where it has regularly undergone painful manipulations it shows no anticipation of them until they start, and its crying ceases as it returns to its mother's arms. It is very different with the child of a year or more, who suffers acutely in anticipation and remembers long. The moral is obvious. I am aware that this teaching goes counter to that of some schools of psychology, who maintain that the earlier an impression occurs the stronger is its effect, but to me the two-year old child with a corrected talipes dashing happily and confidently into the consulting room outweighs a good deal of Viennese dogma. The pain sense is also surprisingly ill-developed in tiny babies. In my young days I worked in a famous orthopædic centre where a new-born baby with talipes was always brought to the surgeon accompanied by a tray of tenotomy knives. The tendo Achillis was cut then and there while the mother held the baby. The babies often seemed quite unaffected by the operation, even if the same could not be said for the mothers.

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delayed until the curious instinct of the very young to do the exact opposite of what their elders demand has begun to slacken.

THE OSSEOUS SYSTEM

Talipes or mouldings of the feet.—It is in the earliness of the sending up of these cases for opinion and treatment that I notice the greatest improvement in general practice in my time. To balance the few cases in which mothers are still advised to "leave it until the baby starts to walk", many are brought within the first few days, with a consequent immense saving of suffering to the patient and of worry to the surgeon. Some of the remaining prejudice against early treatment may be due to the difficulties and disasters inseparable from the use of plaster of Paris on small and wet babies. The pressure can be safely and far more efficiently applied by adhesive felt and strapping on the foundation of a small aluminium footpiece.

Congenital crookedness of the toes, however, is almost always treated as a triviality, and the early treatment put off. My experience is that these ugly little deformities can be cured by treatment begun in the first few weeks of life, and by that alone.

Congenital scoliosis.—There are two types: in the first, abnormalities of the vertebræ themselves are present, such as wedge formations. In the second, there is only a general bending of an otherwise normal spine. In contrast to the deformities of the feet, I have never yet known a scoliosis in a baby sent up for treatment by a general practitioner with any sense of urgency. Yet the urgency is there; to sit up for the first time with a crooked spine is even more disastrous than to stand for the first time on a misplaced foot. The erector muscles on the favoured concave side take the opportunity to go into spasm and outpull their stretched opposers, and the deformity is apt to increase steadily until it finally equals the worst effects of tuberculosis of the spine. To prevent this it is necessary to put the child in a plaster bed at the earliest possible moment, with the spine held in a deformity the opposite of the original one, and to maintain the correction thus gained by exercises that play on the instinctive reaction of the infant to certain positions.

THE ARTICULATORY SYSTEM

Congenital dislocation of the hip.—I have never yet known this condition to be diagnosed at birth; there is no reason why it should not be. Occasionally it is detected, often by a chance X-ray, in the first few months, and then it should be possible to have a normally articulated joint ready for the infant to walk upon when it is wanted. I have recently been very gratified by the success of a method of treatment which dispenses with plaster of Paris, allows free movement with all its benefits, and permits older children to get about the house with much benefit to their tempers.

Congenital stiff fingers.—These can often be much improved by treatment to increase their range of movement. But this treatment must be begun very early.

THE CIRCULATORY SYSTEM

Deformities of the great blood vessels and the heart.—The advisability of delaying these long and intricate operations until increased size and strength make them easier is obvious. A difficulty I have met with myself when operating on the very young is obstruction by a large thymus. On the other hand, the child will not develop normally unless its circulation is made normal, so that a comparatively simple and safe operation, such as the ligation of a ductus arteriosus, need not be delayed beyond the age of five.

Angiomas.—Some of these strange and little understood abnormalities are indubitably congenital deformities: the "port-wine mark" for instance, which remains the same in area throughout life. Other types behave like new growths, and delay in their treatment produces some of the worst and least excusable tragedies of the surgery of childhood. The most dangerous type is one that I have had very little chance of observing in its early stages, because it is quite invariably then treated as a triviality and unworthy of a consultant's opinion. It begins as a small red spot on the face, possibly present at birth, but being noticed with curious regularity when the baby is a fortnight old. The mother is told that it is a scratch or a spot or a little birth mark and that nothing need be done about it. When its rapid growth makes this optimism difficult, the practitioner looks up *nævi* in a textbook and finds that they should be treated with CO₂ snow. He acts accordingly, producing a superficial blister upon a deep growth that may involve the entire cheek, or grossly distort the eye or mouth. It should be taught that a growing red spot upon a baby's face is a surgical emergency.

There is no space in this article to describe the different varieties (at least seven in number) of angioma, nor their different behaviour and treatment. I have found, however, that injections of saturated saline solution have a non-toxic and powerful cauterizing action upon the most dangerous and rapidly growing ones, and will arrest their growth and initiate regression.

THE NERVOUS SYSTEM

Spina bifida.—It should be clearly understood that the only indication for operations upon spina bifida is to improve appearance. No life is ever saved by the removal of a meningocele sac, and only too often by operation paralysis is produced where none previously existed, or an existing paralysis is made worse. Thus a child with incompetent sphincters and paralysed legs is brought for consultation, the grateful mother explaining that its life was saved by a wonderful operation at two days old. The only case that yields satisfactorily to operation is the meningocele with a narrow pedicle and without interference with motor or sensory nerves; and about this operation there is no urgency. It should be realized that meningitis from a leaking meningocele is exceedingly rare, and that thin membranes forming the sac have a strong tendency to thicken and contract. As to the type in which a wide-based sac is covered with skin, with or without a thick layer

of fat over it, this should never be operated upon. The case of meningocele which grows up with paralysis below the lesion and incompetent sphincters is one of the least fortunate of humans. No surgeon should put himself in the position of wondering if he had any part in causing such suffering and humiliation.

THE RESPIRATORY SYSTEM

Hare-lip.—It is occasionally advised that this deformity should be operated upon at the earliest possible moment. I see no advantage in this to offset the lack of development and toughness in the parts concerned and in the baby as a whole. It is hardly necessary to point out that the cleft of the lip has no influence upon swallowing or sucking. The optimum age for operation varies with the type of cleft. If the bone is involved the lip should be joined while it is still soft enough for the cleft in it to be pulled together easily; which means about three months old at the latest. The clefts which are confined to the lip alone may be left almost indefinitely with advantage to the patient and surgeon, although the pressure of lay opinion on the mother usually becomes unendurable after six months or so.

Cleft palate.—Here the time of operation is limited in one direction by the surgeon's difficulties with the very minute subject, and in the other by the need to supply an instinctively working palate for the child when the need of it is felt for speech, and thus avoid the formation of bad habits. Some time between eighteen months and two and a half years is generally satisfactory, and if orthopædic principles are observed in treating the muscles concerned the child should go to school at the age of five talking normally. The need for speech training is a confession of surgical failure; its price is almost invariably self-consciousness and grimacing during speech.

Thyroglossal and branchial fistulæ and cysts.—These are rightly never treated as emergencies of the newborn, although the former is only too often attacked once or more by those who have not studied the anatomy and principles of the operation involved.

Diaphragmatic hernia.—I incline to operate upon this condition as soon as it is diagnosed, because of the liability to strangulation of the prolapsed bowel. Attacks of partial obstruction, at whatever age, are an indication of urgency. With intratracheal anæsthesia and an approach through the chest, the operation, even in infants, is easier and safer than is often thought.

THE DIGESTIVE SYSTEM

Œsophageal atresia.—The surgeon's chance of success in this condition depends upon getting it early, and especially before pneumonia has developed. Over-investigation, particularly the administration of barium swallows, is one of the worst handicaps to the chance of success.

Congenital intestinal obstruction.—Here again the chances of the patient's survival depend mainly upon the earliness of laparotomy. It is very bitter to the surgeon to have submitted for operation a baby hopelessly distended

after ten days or so of "medical treatment", and to find at operation or post mortem some simple mechanical obstruction that could easily have been relieved earlier on. Intratracheal anæsthesia has so diminished the risks of abdominal operations in small babies that the indications for exploration of the abdomen in them are now much the same as in adults.

Deformities of the anus.—These fall into three classes:—

(a) The ectopic or misplaced anus: The most common type is the badly misnamed "recto-vaginal fistula". Its treatment is to incise backwards from the opening and dilate to normal size. This in most cases will produce what I call the "shotgun perineum", in which anus and vagina open side by side without the normal intervening strip of skin. This condition is itself a not uncommon congenital deformity, for which nobody, so far as I know, advocates operation. The various operations for transplanting the anus bodily backwards which can be found in textbooks I believe to be largely fictitious, extremely dangerous, and in any event impossible to perform upon a new-born baby.

(b) The imperfect anus: Here the opening is often so small as to escape observation unless the surgeon knows what to look for. This sign is a tiny spot of meconium, like a fly speck, on the skin, in the normal position or in front of it. But however minute the opening into the bowel which is thus indicated, it carries with it a workable sphincter mechanism, and all that is necessary is to dilate it up to normal.

(c) The imperforate anus: This is an unsolved surgical problem, and perhaps an insoluble one. I incline to think that the best treatment is a spur colostomy of the sigmoid, followed by the attempt to open into the blind end of bowel without destroying the perineal musculature, as is inevitably done by the common approach from below.

THE UROGENITAL SYSTEM

Inguinal hernia.—A satisfactory routine treatment for the common deformity of a persistent processus vaginalis is to control the hernia by a firm rubber (not pneumatic) horse-shoe truss for the first year. By this time the danger of hospital enteritis is much diminished, and the inconveniences of the truss on an actively mobile baby much increased. The truss is removed and in a certain number of cases the hernia never reappears. If it does, operation upon the lines laid down by Hamilton Russell is the only treatment. If the hernia is uncontrollable, operation is the only course whatever the age.

Undescended testicle.—The first step in the treatment of this condition is diagnosis: the separation of the 20 per cent. of congenital deformities from the 80 per cent. of normal variations which are almost invariably classed with them. Once the fact has been grasped that the cavity of the scrotum in the young extends up over the abdominal wall, the "undescended testicle in the inguinal canal" can be left either to nature to descend in the ordinary course of development, or to the endocrinologist to record as a triumph for gonadotrophic hormone. The effect of the latter is the same in

of fat over it, this should never be operated upon. The case of meningocele which grows up with paralysis below the lesion and incompetent sphincters is one of the least fortunate of humans. No surgeon should put himself in the position of wondering if he had any part in causing such suffering and humiliation.

THE RESPIRATORY SYSTEM

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ENDOCRINE DISORDERS AND THE MIND

By V. C. MEDVEI, M.D., M.R.C.P.

Associate Chief Assistant, Endocrine Clinic, St. Bartholomew's Hospital.

CERTAIN experimental investigations of the endocrinology of schizophrenia presented by Hemphill and Reiss (1948) in the Section of Psychiatry of the Royal Society of Medicine, show the interest in the psychosomatic aspect of the function of the endocrine glands. The effect of hormonal imbalance on the mind in major endocrine disorders is known, but has perhaps received less attention than other symptoms. The following survey is meant to stress the frequency of the mental symptoms in endocrine disorders. The examples quoted are mainly based on personal observations.

DISORDERS OF THYROID FUNCTION

(a) *Hyperthyroid states.*—The restlessness and anxiety of patients suffering from Graves's disease is well recognized and sleeplessness is a common feature. Cases which come to attention as psychoneurosis or even frank psychosis are not unknown. In young women, neurotic symptoms may be predominant for a long time—Bauer's "neurothyreosis" (1942). In thyroid crisis, particularly when precipitated by some infection, signs of acute mania and delirium occur.

A woman of forty-two suddenly developed well systematized persecution ideas directed against her husband of forty-four and her daughter of eighteen. As amenorrhœa was present at the same time, her doctor thought of a climacteric psychosis. Loss of weight, attacks of paroxysmal tachycardia, profuse sweating, a moderately enlarged thyroid, an obvious stare, fine finger tremor, a large pulse pressure and a basal metabolic rate of +23 per cent. clinched the diagnosis of thyrotoxicosis. It was not easy to persuade the patient to have an operation. After subtotal thyroidectomy all the symptoms subsided; six months later menstruation returned and was still normal when the patient was seen two years after the operation.

It is quite possible that some of the symptoms of climacteric neuroses and psychoses are due to an imbalance in the production of the pituitary thyrotrophic hormone. Experimental hyperthyroidism in animals may produce nervous excitability apart from loss of weight, tachycardia, sweating and tremor. In human beings it may lead to thyroid addiction with all the symptoms of true drug addiction, as reported first by Patterson (1934). The use of thyroid extract for the treatment of obesity is so widespread, although often useless, that the possibility of addiction is another danger to be borne in mind, before prescribing it without good reason.

A trained nurse of thirty-four developed signs of moderate myxœdema. Her condition appeared to grow worse in spite of energetic thyroid medication. When referred to us she had been taking 15 to 18 grains (1 to 1.2 gm.) of thyroid daily for the last six months. She had some signs of thyrotoxicosis, with the exception of loss of weight (resting pulse of 144-160, basal metabolic rate +30 per cent., tremor, sleeplessness, blood pressure 175/80). It took nearly five years before she very

humans as in rats: to accelerate a process that would in any event have occurred, and to do this at the cost of marked damage to the spermatogenic cells. For the true deformities, the undescended and ectopic testicles, operation should be performed before puberty; probably eight to ten years of age is the optimum time.

Hypospadias.—Here the time indications are fairly obvious. No one would operate for choice upon the tiny penis of an infant; yet the child who goes to school at the age of five unable to pass urine in the normal masculine manner is apt to have his disability brought home to him in a way that will remain with him throughout life. In the severe cases the binding down of the penis should be relieved at the age of eighteen months, and the organ allowed to develop for another two or three years. I have evolved a method by which it is possible consistently to construct a new urethra in a single operation, whatever the degree of deformity. This operation should then be undertaken and the child sent to school on a urinary equality with his fellows.

Extroversion of the bladder.—At present the only treatment for this terrible deformity is the transplantation of the ureters into the bowel. There is no point in doing this until the child has the sense to deal with the new and difficult situation thus produced, and I think about three years of age is the earliest at which the requisite control of the bowel can be expected.

Vesical clefts.—There is an uncommon but well-recognized condition in which the floor of the bladder has not formed, although there is no true extroversion. In the male this shades into epispadias; in the female there is no proper name for the deformity. I have recently had encouraging results in such cases by a method similar to that used in hypospadias, but there is no point in attempting it before the age of three years old at the earliest.

Adherent labiæ minora.—This common condition is, curiously, little recognized. I have many times known cases in which the parents had been told that the vagina was absent, but could probably be constructed at the age of eighteen or so. All that was needed was a single stroke with a probe.

THE MUSCULAR SYSTEM

Sterno-mastoid torticollis.—Here operation is inadvisable until the child is old enough to carry out exercises afterwards. This means waiting until the age of five or so; there is no objection to this, as the facial asymmetry and cervical scoliosis will disappear completely once full range of movement is attained.

THE INTEGUMENTARY SYSTEM

Syndactyly.—This is one of the conditions for which bogus operations are copied from one textbook to another. The only satisfactory treatment is to cover the raw surfaces left by separating the fingers with a skin graft, preferably a full thickness one. Once again, the far from simple little operation need only be done in time to enable the child to go to school in as normal a state as possible.

rare, it is frequent enough to be considered in the differential diagnosis of attacks of unconsciousness and convulsions. Levrat and Brette (1947) quote seven cases of spontaneous parathyroid tetany, in two of which syphilis was the cause; in two others there was chronic tuberculosis; in one a traumatic meningitis was responsible. The typical clinical picture of parathyroid tetany resembles a mental affection, i.e., a fit. Afterwards the patients are usually irritable, easily upset, and display signs of deep anxiety, forgetfulness and headaches, apart from any concurrent mental symptoms due to the underlying disease. Such minor mental changes are liable to become permanent unless the attacks completely disappear. In early stages of parathyroid deficiency the picture of a toxic psychosis with delirium may be the first symptom (Greene and Swanson, 1941).

Fits, epileptiform and "hysterical" attacks after any operation or trauma, particularly in children, may be in fact attacks of secondary parathyroid tetany caused by a sudden disturbance of the calcium metabolism.

A woman of thirty-four suffering from fibrocystic disease, had a parathyroid adenoma removed successfully. A few hours after the operation she developed parathyroid tetany ending in a confused state, but was relieved eventually by calcium. As the blood and urine calcium content had not changed compared with the readings before the operation, it was assumed that the decalcified osseous tissues might have drawn calcium from the nervous tissue (brain) thus causing the fit and the mental confusion.

DISORDERS OF THE ISLETS OF LANGERHANS

(a) *Hyperglycæmia* does not, in itself, cause mental disturbance. On the contrary, persistent emotional upset may play an important part in producing hyperglycæmia.

(b) *Hypoglycæmia*.—Any form—primary due to an insuloma, secondary caused by an overdose of insulin, and spontaneous due to other causes—may show mental symptoms of almost any type. Psychoneurosis, anxiety states, impaired memory, hallucinations and delusions with persecution ideas and acts of violence, occur followed by complete amnesia. Convulsions, mental confusion, emotional instability and schizoid features, particularly catalepsy, have been described (Wilder, 1940).

A middle-aged woman came under our care because she had been repeatedly arrested by the police for drunkenness and unconsciousness followed by disorderly and insulting behaviour at the police stations. The attacks occurred when queuing-up early in the morning after a hasty cup of tea. She was teetotal and greatly upset by her experience. An islet adenoma was successfully removed, and prevented further trouble with the police.

In another case, a youngish man developed what appeared to be persecution ideas directed against his office superiors, particularly in the late morning. The solution proved to be that he was a diabetic who had not told this fact to his employers because he was (wrongly) afraid of losing his job. He had his combined insulin injection at 6 o'clock in the morning.

DISORDERS OF THE ADRENAL GLANDS

(a) *Primary hyperfunction of the cortical tissue*.—The fact that hyperfunction

gradually and reluctantly had her thyroid intake reduced to $\frac{1}{2}$ a grain (32 mgm.) twice daily, which kept her myxœdema easily under control. As a nurse she had access to thyroid and was convinced that she could not keep awake and working-fit unless she took the thyroid in large amounts. The reason why so many people do not develop more serious symptoms of this artificial hyperthyroidism is, in my opinion, due to the formation of antihormones.

(b) *Hypothyroid states*.—The lethargy, apathy and sleepiness of the myxœdematous patient, with increasing slowing of speech and intellectual processes and failing memory, are accepted as classical symptoms. That they may not be readily recognized if they occur in old age and in unusual circumstances will be seen from the following observation:—

A female patient of over seventy went abroad for several months to escape the rigours of the winter. While away she fell ill, complaining of giddiness, headache, "slurring of speech", failing memory, depression and change of mentality; she became suspicious and had occasional attacks of delirium. Her daughter consulted a well-known medical man abroad. In view of her age, of an appropriate sclerosis of her vessels, and of the fact that he had not known the patient before (nor spoke her mother tongue sufficiently well to be able to judge the alteration of speech) he diagnosed "cerebral arteriosclerosis" and sent her home. The change in her previously high intellectual capacities, the only moderately raised blood pressure, the lack of focal symptoms, the type of change in her speech, the complaint of vague rheumatic pains all over the body, the feeling of cold, the puffiness of her face, and a high blood cholestesterol enabled us to make the tentative diagnosis of myxœdema. On thyroid medication she recovered completely in three months.

Mild myxœdema is sometimes masked by anxiety and schizoid states.

Zondek and Wolfsohn (1944) described a case of a woman of twenty-three who developed myxœdema after normal childbirth with additional mental changes characteristic of schizophrenia (hallucinatory psychosis). After eighteen months the correct diagnosis was made. On large doses of thyroid she recovered completely within two weeks and was perfectly fit one year later. At the time of the rapid improvement the only striking physical change was an increase in output of urine and sodium chloride. It is suggested that the favourable effect was due to dehydration of the cerebral tissues.

A woman of thirty-four had undergone a subtotal thyroidectomy by Sir Thomas Dunhill for attacks of paroxysmal tachycardia and signs of a moderate thyrotoxicosis. Three months after the operation she apparently suddenly developed a hallucinatory psychosis with delusions. Her doctor was away and his deputy thought first of barbiturate poisoning, then of psychosis. When seen by us she had unmistakable signs of myxœdema and recovered on thyroid within a week. She had to continue taking small doses of thyroid on and off for the next three years, particularly in the winter, before the last traces disappeared.

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(a) *Hyperparathyroidism*.—Hyperparathyroidism caused by primary hyperplasia of the parathyroid glands is rare. In these cases irritability and nervous confusion have been observed. In the more frequent cases of secondary hyperplasia, usually associated with chronic renal disease, the existing apathy and stupor are more likely an expression of renal failure and chronic acidosis. In acute parathyroid poisoning, due to accidental administration of excessive amounts of parathormon, depression and listlessness were observed in a boy by Lowenburg and Ginsburg (1932).

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than 300 mm. Hg. At the second of two operations a left phæochromocytoma was found by Leriche in December, 1933, and successfully removed. The case was described later in detail by Bauer and Leriche (1934).

(c) *Adrenal cortical insufficiency*.—In Addison's disease the weakness and general debility is sometimes mistaken for a depressive state. An acute attack or crisis may be accompanied by acute mental confusion.

One of our patients with Addison's disease was a woman of fifty-four, who had the first symptoms of illness in January 1933. She was admitted to a mental hospital in October 1933 in a state of mental agitation and confusion. She died in June 1934, and the post-mortem examination confirmed the diagnosis. One of her brothers had been buried under debris in the 1914-18 war. In 1922 he had a "nervous breakdown", following which he developed a typical Addison's disease. This diagnosis was confirmed by Falta at his hospital. The patient died of it in 1924 at the age of forty-two (Medvei, 1935).

It is possible that the hypoglycæmia is partly responsible for the obvious mental symptoms in some cases.

DISORDERS OF THE GONADS

(a) *Precocious puberty*.—Only cases which are caused by abnormal gonadal function alone are discussed here. In boys under six the outstanding feature is the increased libido without the normal inhibitions of an adult, and with an intelligence often far below the mental age. They may, in some ways, resemble the young apes and monkeys studied by Zuckerman (1932). In boys with hyper-interrenal precocity Goldzieher (1944) found that their mental state corresponded to their actual, rather than to their apparent age. Psychoneurosis due to conflict between sexual development and mental immaturity is quite common (such features occur also in young apes).

Girls show occasionally an intelligence a few years in advance of their real age and an emotional life in accordance with their precocious sexual development. This applies particularly to cases in which no granulosa cell tumours or other organic pathological changes can be found. Such patients may develop into normal adults without any disorder ever being discovered, provided they are sheltered from premature experience of sex life.

One girl who belongs to this group was observed by us from the age of four until the age of nine. At four she had the physical and emotional characteristics of a well-developed girl of thirteen; at nine those of one of eighteen. Although no strict intelligence tests were applied, she was in intelligence at least five to six years ahead of her age.

In certain very rare cases of tumours of the interstitial cells of the testicle occurring in boys, precocious sexual development may be accompanied by precocious intelligence (Rowlands and Nicholson, 1929). Removal of the tumour may stop the premature development, with or without retrogression.

Equally rare are granulosa cell tumours in young girls. Parks (1938) reported on a girl of five with precocious sexual development including menstruation. Although the face looked old for her age, intelligence was above average and emotional life normal for her age. Removal of the tumour resulted in complete retrogression and recovery. At the age of nine she

of the cortical tissue may lead to virilism in women and occasionally to feminization in men is in itself sufficient to explain the severe mental stress to which such people are exposed. In children, before the age of puberty, homosexual traits may exist; in grown-up women the mere fact of change of appearance may lead to neurasthenia. This, however, is not the whole story: Clifford Allen discusses 52 cases he has analysed, and concludes:—

"Failure of the endocrine factor (i.e. abnormal function) such as occurs in adrenal virilism prevents, or may prevent, the normal psychical development.

"Correction of the adrenal factor (and presumably other endocrine dysfunction in other diseases) may lead to this restoration of normality.

"Some cases of adrenal virilism show a lack of sexual interest in others and a concentration of interest on to the self which we have called autosexuality.

"Less severe conditions lead to a lack of development which shows itself as homosexuality" (Broster, Allen, *et al.*, 1938).

Our own observations confirm these views. Of interest is perhaps the case of a girl of nine with adreno-cortical virilism who showed certain traits characteristic of boys of ten to thirteen (Bauer and Medvei, 1932).

A further proof of Allen's views seems to be given by the following cases:—

Mathias (1922) described two sisters of forty-two and somewhat younger with all the signs of virilism since early youth. A post-mortem examination of the first showed hyperplasia of the cortex. The other had a laparotomy. Both had homosexual tendencies. On the other hand, two sisters with adreno-genital virilism, of twenty-one and nineteen, observed by Loeser and Israel (1923) were apparently both heterosexual. In Holl's (1930) case of feminization of a man of forty-four, loss of libido and potency accompanied the physical signs of gynæcomastia, obesity, and testicular atrophy. After surgical removal of a cortical tumour there was a complete reversion to normal. Similar experience was observed in the case described by Simpson and Joll (1938).

The symptoms of mental depression may be so marked in cases of the adreno-genital syndrome as to be mistaken for true melancholia.

A young Italian girl developed with the signs of virilism a serious depressive state with feelings of guilt and self-reproach. She regarded her condition as Divine punishment for having broken her engagement to her soldier-fiancé.

In Cushing's syndrome mental depression is almost the rule, as will be discussed later.

(b) *Phæochromocytoma of the adrenal medulla.*—The attacks of paroxysmal hypertension of over 300 mm. Hg occur often at odd times and are liable to be mistaken for neurasthenia.

The case of a Roumanian engineer of forty, a highly strung batchelor, is of interest. He complained of attacks of sinking feeling and malaise in the epigastrium, slight nausea, pallor of the face and hands which felt cold and clammy, palpitations, pulsation of his eyeballs, cold sweat and sometimes slight finger tremor. These attacks occurred almost always between 3 and 4 a.m., rarely at 5 a.m., and were not relieved by previous or concurrent intake of sugar which had been suggested. He had never been seen in one of these attacks, described by him most dramatically. When I was called as the duty officer one morning at 2.30 a.m. in May 1933, my first indignant impression was that of a grave neuropath with chattering teeth, anxious facial expression, clammy hands and slight tremor, who in spite of this display quite calmly described his feelings in terms like: "Now I feel as if my eyeballs would jump out of their sockets". Sleepy and cross though I was, I woke up immediately when I felt his pulse. The sphygmomanometer did not register more

than 300 mm. Hg. At the second of two operations a left phæochromocytoma was found by Leriche in December, 1933, and successfully removed. The case was described later in detail by Bauer and Leriche (1934).

(c) *Adrenal cortical insufficiency*.—In Addison's disease the weakness and general debility is sometimes mistaken for a depressive state. An acute attack or crisis may be accompanied by acute mental confusion.

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DISORDERS OF THE GONADS

(a) *Precocious puberty*.—Only cases which are caused by abnormal gonadal function alone are discussed here. In boys under six the outstanding feature is the increased libido without the normal inhibitions of an adult, and with an intelligence often far below the mental age. They may, in some ways, resemble the young apes and monkeys studied by Zuckerman (1932). In boys with hyper-interrenal precocity Goldzieher (1944) found that their mental state corresponded to their actual, rather than to their apparent age. Psychoneurosis due to conflict between sexual development and mental immaturity is quite common (such features occur also in young apes).

Girls show occasionally an intelligence a few years in advance of their real age and an emotional life in accordance with their precocious sexual development. This applies particularly to cases in which no granulosa cell tumours or other organic pathological changes can be found. Such patients may develop into normal adults without any disorder ever being discovered, provided they are sheltered from premature experience of sex life.

One girl who belongs to this group was observed by us from the age of four until the age of nine. At four she had the physical and emotional characteristics of a well-developed girl of thirteen; at nine those of one of eighteen. Although no strict intelligence tests were applied, she was in intelligence at least five to six years ahead of her age.

In certain very rare cases of tumours of the interstitial cells of the testicle occurring in boys, precocious sexual development may be accompanied by precocious intelligence (Rowlands and Nicholson, 1929). Removal of the tumour may stop the premature development, with or without retrogression.

Equally rare are granulosa cell tumours in young girls. Parks (1938) reported on a girl of five with precocious sexual development including menstruation. Although the face looked old for her age, intelligence was above average and emotional life normal for her age. Removal of the tumour resulted in complete retrogression and recovery. At the age of nine she

was a happy, intelligent and perfectly normal girl.

(b) *Castrates and eunuchoids (and the menopause).*—Castrates may be male or female. If the gonads of normal healthy boys are removed artificially before puberty, they are termed eunuchs. A eunuchoid is a male with gonadal hypofunction due to other causes than castration (the term female eunuchoid is used, but is etymologically an unhappy one). Castration of a fully developed adult male may not cause any mental or emotional disturbance.

A man in his fifties came under my observation for some chronic ailment. He had had a double orchidectomy for tuberculosis at the age of about twenty-eight. At that time he was married and had already two children. The very shrewd and experienced surgeon put a lump of wax into the scrotum, thus giving the man the impression that some gonadal tissue remained. When I saw him twenty-five years later it appeared that he had been able to lead a fairly normal, though placid, married life. This case confirms Clifford Allen's dictum that "sexuality is a complex matter dependent on endocrine and psychological factors", whereby the psychological machinery is partly inherited and partly acquired. On the knowledge of this fact was based a risqué French comedy between the wars, but much preceded by Wycherley's "The Country Wife" in 1675.

Eunuchs show signs of mental apathy, but the general intelligence is not always impaired. Many of them are clever and more often shrewd. In Byzantium and the Middle East many of them achieved political power and high positions. Narses, the "elderly Armenian eunuch" showed his valour on the battlefield of Gualdo Tadino (552) and as the first Exarch of Ravenna (Viceroy of Italy), "a good soldier and most prudent statesman" (H. A. L. Fisher, 1936). This applies even more to eunuchoids, among whom artistic and scientific abilities may be very highly developed.

Emotionally, eunuchoids are usually autosexual and self-centred and become more so with the decline of their scantily developed sexual functions. They often pretend to have heterosexual interests and many of them get married, indulging in detailed descriptions of their sex life. With the increasing autosexuality goes often an intense ambition. ("Autosexuals are interested only in themselves. They show no capacity for loving anyone other than themselves. Complete egocentricity marks them". Clifford Allen, 1938.) They long for opportunities for showing off, either by particular attention to their appearance or by obvious and exaggerated neglect of it. This coincides in some cases with frank schizophrenic traits. McCartney (1929) found the 23 cases of castrates he studied, introspective and apathetic, with typical schizoid characters: "They could talk intelligently but appeared stupid, were methodical but usually not purposeful, and were cold, passive and moody". With increasing age true melancholia with suicidal tendencies and self-reproach develops in some cases. Obsessional and persecution ideas, often following exaggerated and thwarted ambition, are frequent, a feeling of frustration common. The emotional instability of these patients is expressed by the fact that all of them are neurotic, except when their neurosis is overshadowed by more profound mental deviation. The division of eunuchoids into two bodily contrasting groups by Tandler

and Grosz (1913) is also reflected in the mental types: the tall, thin ones with graceful movements tend to show schizoid traits and are artistic, if intelligent. The obese, short eunuchoid is lazy, depressed, but practical. Administration of methyl testosterone in sufficient doses may have a profound effect on the mental condition of such patients, making them cheerful, interested and sociable (Kearns, 1941).

In women, castration brings about the signs and mental changes of the menopause. The female menopause is in a way comparable to a physiological castration (but not entirely so). The mental changes of the climacteric have been carefully and extensively studied in both sexes (Werner, 1945) and do not need a detailed discussion here. The most important are anxiety, nervous tension and irritability. Their extent depends upon the previous nervous make-up of the individual. Primary amenorrhœa due to lack of œstrogenic stimulation and consequent under- or non-development of the uterus leads almost always to neurosis and occasionally to depression. The beneficial effect on the mind following the production of even one or two œstrone withdrawal bleedings is surprising, and such treatment is well worth the attempt.

(c) *True hermaphrodites*.—These are extremely rare. They are better called male and female gonadal intersexes, as they are genetically pre-determined men or women with partly functioning tissue of both types of gonads. The mental condition of these individuals is too complicated to be discussed in the present survey. They have been investigated extensively by various authors to whom reference should be made. Neugebauer's (1908) classic on the subject has been added to, brought up to date, as it were, and discussed in the light of modern ideas by Cawadias (1948) in a more recent monograph.

DISORDERS OF THE PITUITARY GLAND

(a) *Acromegaly*.—The expression of apathy and depression is characteristic of the appearance of many acromegalics. Even dogs with experimentally produced acromegaly look mournful and behave so. True melancholia, however, is very rare. Usually apathy prevails and this causes the pathetic facial expression, together with the physical changes. At the onset irritability may be present, and in one of our patients this was the first symptom noted by his family.

He used to be a very quiet and peaceful man of thirty, who suddenly complained of severe headaches and became forgetful. This made him extremely irritable. He tried to give vent to his feelings by angry speech and gestures, but he could not get the words out of his mouth properly: "It seemed as if his tongue would choke him". This contrast produced a comic appearance and first drew attention to the other changes.

In progressive cases delusions and persecution ideas may occasionally develop. In older patients such symptoms are made worse by the concomitant impotence and loss of sexual function.

(b) *Fröhlich's syndrome*.—When presenting his original case to the Vienna

Medical Society in 1901, Fröhlich expressly remarked: "Appetite and sleep good. Intelligence and speech quite normal (1901)". This was after two years' continuous observation since the onset of symptoms. If, on the other hand, the "Fat Boy" in Dickens' "Pickwick Papers" is often quoted as a typical representative of Fröhlich's syndrome, with his mental backwardness, dullness, sleepiness and his enormous appetite; these are no doubt hypothalamic symptoms. Many fat boys, wrongly termed "Fröhlich's type" are simply lazy.

(c) *Cushing's syndrome (due to basophil adenoma)*.—In all seven cases of our own observation, four of which were confirmed by autopsy, signs of melancholic depression of varying degree were present. Five patients were examined by the psychiatrist, and he was of the opinion that the mental condition in all these cases was a true depressive psychosis. This suggested to us the addition of the mental change as an important symptom to the polymorph symptomatology of Cushing's (basophil) syndrome. Such a view seems confirmed by the case (with autopsy) of Schlezinger and Horwitz (1940), who found a depressive psychosis and an extrapyramidal disorder. I feel certain that careful investigation will elicit the presence of these symptoms even in milder forms. They are found only rarely in cases of primary hyperfunction of the adrenal cortical tissue, but do not occur regularly or typically. They may be added to the group of physical symptoms evaluated in an attempt to distinguish clinically between Cushing's syndrome due to basophil adenoma, cases of adrenal cortical tumours, and of arrhenoblastomas of the ovary (Medvei and Wermer, 1934).

(d) *Simmonds's disease*.—The term is used as an alternative to pituitary cachexia. Mild forms, running a more chronic course, are called anterior pituitary insufficiency. Some cases of Simmonds's disease begin with irritability and excitability followed by extreme weariness. This is often explained away by the difficult childbirth and the post-partum hæmorrhage which start the trend of events. In other cases abnormal sleepiness, slowing of speech and of reaction time, carelessness and neglect in personal appearance are first observed. With the increasing apathy anorexia appears. The loss of sexual function is preceded by the loss of libido. When the disease progresses the mental dullness may pass into stupor. In later stages this stupor is sometimes suddenly interrupted by a short phase of confusion with excitability and disorientation, often ending in collapse and death.

It is almost unbelievable to see such a patient, who has become extremely emaciated and almost unable to move or lift a finger, suddenly rally unexpected powers for a few minutes, in a state of violent confusion, usually combined with the expression of grave anxiety, fear and attempts to get up and away. Then the asthenia supervenes and the patient succumbs in a hypoglycæmic attack.

Obviously, the mental condition, like the physical, is much influenced by the marked adrenal cortical deficiency, by the disturbance of the carbohydrate metabolism leading to severe hypoglycæmia, and by the atrophy of the thyroid and the gonads: men are rarely affected. If so, the disease is often of a milder form and sometimes masquerades as myxœdema. In men the

destruction of the anterior lobe of the pituitary may have been caused by a chromophobe adenoma. The mental changes are similar to those mentioned, although perhaps less severe. It is important to stress the fact that in most cases of Simmonds's disease there is no history of psychoneurosis previous to the illness—in contrast to anorexia nervosa.

(e) *Pituitary dwarfism*.—These patients have usually a normal mentality, good intelligence and are alert and active. Many of them, particularly male patients, are sweet tempered. This is the most appropriate phrase to apply. The main disturbing factor is the lack of sexual development; it seems to them much more important than their stunted growth.

In one of our patients aged over twenty a uterine bleeding—the first in her life—was produced by implantation of 50 mgm. of oestradiol. The mental reaction was so overwhelming and pathetic that it made us feel uncomfortable. The treatment appeared doubly justified, however, when it was seen that the reaction was transmitted to the trained nursing staff and reflected back to the patient. In another case of a woman of twenty-nine, the family doctor became the innocent cause of enhanced happiness to the patient, by his profound surprise and admiration for the transient hormonal effect of an oestrogen withdrawal bleeding.

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season begins. Owing to the fluctuation in intensity of the pollen cloud from day to day, maintenance doses of pollen extract should be continued until the season is over. It is sometimes recommended that patients should be taught to give themselves their own injections, but if this plan is followed the serial dilutions must be made to progress very slowly in order to avoid the risk of a reaction when the patient is away from the doctor. This will necessitate many injections, perhaps 40 or more, and it is likely that some individuals will not have the patience required to complete the course.

Treatment is usually effective for one season only, and in many cases must be repeated each year indefinitely. In a proportion of patients it appears that some lasting protection is conferred after a few years' treatment, which may then be discontinued.

TABLE I

<i>Grass pollen Dose No.</i>	<i>Strength of Solution</i>	<i>No. of Pollen Units ("Noon units")</i>	<i>Dose in ml.</i>
March {	100 units in 1 ml. or 1 in 10,000	10	0.1
	"	15	0.15
	"	30	0.3
	"	50	0.5
	"	80	0.8
	1,000 units in 1 ml. or 1 in 1,000	100	0.1
April {	"	150	0.15
	"	300	0.3
	"	500	0.5
	"	800	0.8
	10,000 units in 1 ml. or 1 in 100	1,000	0.1
	"	1,500	0.15
	"	3,000	0.3
	"	5,000	0.5
	"	8,000	0.8
	50,000 units in 1 ml. or 1 in 20	10,000	0.2
May {	"	15,000	0.3
	"	30,000	0.6
	"	50,000	1.0
	100,000 units in 1 ml. or 1 in 10	75,000	0.75
	"	100,000	1.0
	"		

Then 50,000 units once a week until mid-July. Pre-seasonal injections should begin on March 1, and be given twice weekly.

THE TREATMENT OF HAY FEVER

By NEVILLE SOUTHWELL, M.D., M.R.C.P

From the Clinic for Asthma and Hay Fever, Guy's Hospital.

The condition known as hay fever is an allergic response of the mucous membrane of the nose and eyes to various wind-borne pollens. In England, by far the most important of these pollens are the pollens of grasses: much less important are the pollens of certain trees and a few weeds. The heavy and sticky pollens of flowers are insect-borne and only produce symptoms of hay fever by close contact. Broadly speaking, the trees pollinate first, in early spring; the grasses next, in late spring, early and mid summer; and the weeds last, in summer and early autumn. In southern England the all-important grasses pollinate from the third week in May until the third week in July, and it is therefore mainly during this period that the symptoms of hay fever occur.

SKIN TESTING

Although an extremely controversial method of investigation in asthma, skin testing is a valuable confirmation of clinical assumptions in all cases of hay fever. Commercial pollen extracts are available, and 0.05 ml. should be injected intracutaneously, using a small needle and a tuberculin syringe, *on the flexor surface of the forearm*. Skill is required in the interpretation of the results, which should always be considered in conjunction with the clinical features of each case, and against the results of a control injection of normal saline.

It is generally agreed that although the various grass pollens are of different botanical composition in each individual species, they share a large measure of antigenic identity. It is therefore probably sufficient in those cases with a clear-cut history of symptoms only during late May and throughout June to skin test and, if necessary, to desensitize with not more than one or two representative grass pollens, and for this purpose the pollen of Timothy grass or cocksfoot is commonly employed (e.g. "pollacine": Parke, Davis and Co.). There are, however, those who prefer to treat their patients with mixed extracts of a large number of the commoner pollens (e.g. Bencard's combined pollen vaccine). In the minority of cases in which the seasonal incidence or environmental history suggests that pollens other than grass pollens may be producing symptoms, those trees or weeds suspected must be tested for separately.

SPECIFIC DESENSITIZATION

It is best to adopt a pre-seasonal desensitization programme, which should be planned well in advance of the hay fever season in order that the patient should be able to tolerate the highest dose of pollen extract just as the

such as giddiness or nausea. Weakness, dry mouth and dyspepsia occur occasionally.

Dosage.—If anthisan is used it is best to start treatment with 0.1 g. thrice daily, and if symptoms are not controlled double the dose to 0.2 g. thrice daily. This is usually adequate, but if not, 0.3 g. thrice daily may be given. If this is still unsatisfactory then try benadryl or antistin.

There is one rather serious disadvantage which may follow the use of antihistamine drugs. In certain cases it seems that when the effect is very successful pollen asthma may appear for the first time, presumably due to the ease with which pollen is inhaled into the bronchial tubes instead of being obstructed by the swollen nasal mucous membrane. It is clearly desirable therefore to advise specific desensitization whenever possible as well as antihistamine therapy in all cases of moderate or severe nature; only in cases of mild degree may antihistamines alone be employed, and even then the appreciable risk of the development of hay asthma in the future is a strong point in favour of using specific therapy also in these cases.

OTHER MEASURES

Very little general advice of any value can be offered. It is wise to restrict motoring so far as possible, and country trips or visits to cricket matches and the like are foolish. It is remarkable how stupid many patients are over these obvious precautions. Dark glasses are often a help, and the following local applications may prove of value:—

For the nose: Ephedrine hydrochloride	..	10 grains (0.65 g.)
Procaine hydrochloride	..	5 grains (0.32 g.)
Menthol	..	5 grains (0.32 g.)
Eucalyptus oil	..	3 grains (0.2 g.)
Peppermint oil	..	1 grain (0.065 g.)
Soft white paraffin	..	to 1 ounce (28.4 ml.)

Smear the ointment in the nostrils on rising, and several times during the day.

For the eyes: Antistin-Privine (Ciba), 1 drop in each eye every three hours.

RESULTS OF TREATMENT

Widely varying claims have been made on behalf of specific desensitization, but in my own experience less than half of all cases have achieved anything like a satisfactory prevention of symptoms. Even these patients can never with impunity walk down a country lane in June. Of the remainder, a number of patients report some improvement, but a disappointing proportion obtain absolutely no benefit at all. With the additional use of the antihistamine drugs the results of treatment are very much better. The combined effect of specific therapy together with an antihistamine preparation produces great relief in the overwhelming majority of patients, and if local treatment is also employed on occasions of particular exposure to pollen, it should be altogether exceptional for any patient not to obtain substantial relief from this distressing complaint.

Technique.—Every injection should be carefully measured, and introduced under the skin of the outer and upper part of the arm or leg. It will be found that most patients are sensitive to grass pollen only, in which case several reliable commercial extracts of Timothy or mixed grass pollen are available. When it is necessary, extracts of other individual pollens can be prepared comparatively quickly. A scheme of dosage is suggested for the usual grass-sensitive patient (table 1, p. 149).

Side-effects.—However carefully the scheme is conducted, in some patients of a large series ill-effects may follow the injections. These are usually the minor complaints of slight local swelling of the arm or trifling malaise, and need not cause alarm. Occasionally a very severe reaction occurs, taking the form of collapse, difficult breathing and urticaria. This may be extremely dangerous and fatal cases have been reported. At the first sign of such a reaction inject as promptly as possible 1 ml. of 1:1000 adrenaline into the muscle of the deltoid. If it is available give a full dose of an antihistamine preparation by mouth, either 0.3 g. of anthisan or 0.1 g. of benadryl. Be prepared to repeat treatment with adrenaline if necessary. These major reactions are usually, but not always, due to errors in the amount or in the spacing of the pollen extract injected. Do not increase the dose after a patient has missed an injection, nor after any but the mildest side-effect. When changing from a weak dilution of large bulk to a more concentrated dilution take particular care, and do not let the patient leave your waiting-room for half an hour after his injection, as should a severe reaction occur it will do so within this period.

ANTIHISTAMINE SUBSTANCES

In practice, the benefits of an antihistamine preparation are often remarkable. It may be possible to control symptoms completely; and there is the advantage of oral administration. The substances may be used as an adjuvant to specific desensitization, or in place of it in cases when the patient attends too late in the season to begin pre-seasonal desensitization, or when the symptoms are not considered sufficiently severe to warrant the adoption of specific therapy. Antihistamine drugs will also be of value in cases in which specific therapy has proved ineffective.

There seems to be little to choose between the efficacy of the different preparations. Patients vary in their individual responses and if one substance is unsatisfactory it is worth while to try one of the others. My own preference is for anthisan, which I believe to be on the whole less productive of side-effects than the others and equally, or perhaps even slightly more, effective.

Side-effects are numerous but not dangerous. Drowsiness is the most common complaint, and this usually lessens if the patient perseveres with the drug. If it does not, 5 mg. of *d*-amphetamine sulphate in the morning will be helpful, and will also serve to diminish other possible side-effects,

such as giddiness or nausea. Weakness, dry mouth and dyspepsia occur occasionally.

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CURRENT THERAPEUTICS

XIV.—THE USE OF SYNTHETIC PLASTIC MATERIALS IN SURGERY*

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A CRITICAL review of the literature pertaining to the use of synthetic plastic materials in surgery was made in 1947 by Ingraham, Alexander and Matson. The report dealt almost exclusively with synthetic plastics which had been implanted in human and animal tissues. Because of the significance of plastic materials, which has continued to grow, the present article summarizes briefly the information already reported, and presents in addition the data available in the literature since the previous review. A complete bibliography is appended.

PLASTIC MATERIALS AND THEIR PROPERTIES

Only the synthetic plastics or resins have been useful in surgery: other industrial plastics, known as natural resins, cellulose derivatives and protein substances, have not proved to be of permanent value from the surgical point of view and only brief reference will be made to them.

A synthetic plastic is an organic material which, through the application of pressure or heat, can be made into almost any desired shape. More carefully defined, it is a solid which contains an organic substance of large molecular weight which in some stage of its manufacture, or in its conversion into end-products, is capable of being shaped by flow. The synthetic resins in surgical use possess relatively simple chemical structures, are resistant to atmospheric and chemical corrosion, and present high structural strength with light weight. Synthetic plastics may be either thermosetting or thermoplastic. The thermosetting materials are made extremely hard by heating and are used extensively in industry. "Bakelite" is an example of such a plastic. So far these have not been useful in surgery. Thermoplastic materials melt when heated and solidify when cooled. The extremes of

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temperature reached in human and animal tissues are not sufficient to alter the physical properties of these compounds.

Since many industrial synthetic thermoplastic materials are of high molecular weight and are hard and brittle at ordinary temperatures, certain compounds known as plasticizers, among which are camphor, tricresyl phosphate and glycerol, are added to increase their flexibility. As some of these processes are commercial secrets, the addition of such plasticizers renders difficult the problem of obtaining standard plastic materials for use in surgery. Furthermore, the plasticizers have a tendency to become separated from the plastic in which they are mixed, particularly in the presence of solvents. The use of plasticized synthetic materials in human tissue cannot therefore be recommended for three reasons: (1) the uncertainty of obtaining a standard product; (2) the possibility that plasticizers released in tissues might be noxious; (3) the likelihood that the physical properties of synthetic plastics might be altered significantly with the release of plasticizers in the body tissues.

Synthetic substances to be buried in human tissue should meet the following criteria: (1) they should not be physically modified by tissue fluid; (2) they should be chemically inert; (3) they should not excite an inflammatory or foreign body response in the host tissue; (4) they should be non-carcinogenic; and (5) they should be non-epileptogenic when buried in brain tissue.

SURVEY OF THE SYNTHETIC PLASTICS

Vinyl resins enjoy wide popularity commercially under the common trade name of "vinylite". These compounds, of which there is a great variety, attain pliability by the addition of plasticizers, and as a consequence it is difficult to obtain standard products. Certain of these materials have been found to be well tolerated by animal tissues but, because of the difficulties already mentioned, they cannot be recommended for use as material to be buried in human tissue. They have been used extensively for endotracheal catheters and as a substitute for rubber in intestinal intubation and for intravenous tubing. "Portex" is a vinyl compound used extensively and with great satisfaction in England for some of the purposes mentioned above.

Cellulose plastics.—These plastics were among the first to be utilized by industry and formed the basis for the modern plastics industry. They are generally sold as cellulose acetate and cellulose nitrate, usually with the addition of some form of plasticizer or with a special chemical coating to give particularly desirable physical properties. They are popularly known as "cellophane" and "celluloid", and their well-known properties of pliability and transparency have prompted some surgeons to use them in joints, as a covering for the brain, and around the site of a nerve suture. The controversial nature of the literature available on this subject is attributable to the fact that there are many different types of cellophane, and

it is rare for two investigators to obtain the same material from commercial sources. Those workers who have performed carefully controlled experiments, including histological studies of tissue reaction, have found cellophane extremely irritating to human and animal tissues. This material is suitable for use in surgical procedures only when local scarring is required, such as in the obliteration of vascular channels, or experimentally for the production of hypertension in animals by wrapping the kidney in cellophane. Celluloid, likewise, is a tissue irritant. Although it has in the past received extensive use in cranioplasty, it has been superseded by various materials which possess superior physical properties and which produce little or no tissue reaction.

Miscellaneous plastics.—The sporadic use of various plastics in surgery has been reported. These have included substances referred to simply as "plastic materials", materials allied to "bakelite", protein substances, and certain alginates. In general, these have not been documented by adequate experimental trial and cannot be considered as satisfactory for surgical use unless further experimental work is published.

There remain three synthetic plastic materials about which an adequate amount of experimental and clinical data is available. They can all be obtained in standard form and they produce minimal tissue reaction.

NYLON

The term "nylon" is a generic term applied to a large family of related chemical compounds. It does not refer to a single pure product. These products are widely used as filaments to fabricate stockings, parachutes and other materials formerly made of silk. The plastic can be extruded readily or moulded into various forms, but it is in the form of a filament that it has received most extensive surgical use as a suture material. In all probability the various nylon sutures supplied by commercial medical supply firms are not identical products chemically but, regardless of this seeming lack of standardization, all studies of tissue reaction caused by suture material made of nylon have been favourable. It is resistant to chemicals, withstands repeated autoclaving, and possesses great strength and elasticity. It is stronger than silk, strand for strand, but, because of its inherent elasticity, knots tied with nylon have a tendency to slip. Because of this quality it has not been universally acceptable as a suture material.

Nylon can be produced in the form of tubes or sheets, but so far no experimental studies have been reported on its use in this form. It has been used as an occlusive dressing to prevent contamination of wounds by secondary invasion of bacteria from the outside.

METHYLMETHACRYLATE

This compound is known as "lucite" or "plexiglass" in the United States and as "perspex" or "acrylic" in England. It is obtained by the polymerization of derivatives of acrylic acid, which under the influence of certain

catalytic agents go through various stages to form methylmethacrylate. In its fully polymerized form it is a standard product, and is said to exist in the form of chains made by the linking together of the original monomeric molecules. This compound, in its finished form, is a hard tough substance with high tensile strength which can be turned out in the form of sheets, rods or tubes, or moulded into any desired form. It is light, has a low specific gravity, is chemically inert and stable, has almost no water absorption, is transparent and clear, and is non-porous to bacteria. It is unchanged by human or animal tissues and is well tolerated by them.

A large amount of experimental and clinical information is available regarding this plastic. In addition to its common use in dentures, it is very satisfactory for the repair of skull defects. It is not irritating to brain tissue and various methods have been devised for the rapid production of proper moulds which facilitate its use in one-stage cranioplasty. It has also been used in arthroplasty, in the production of moulded implants for the correction of facial deformities and deformities of the eyelids, in the production of artificial eyes, and in extrapleural pneumolysis for tuberculosis, using lucite implants within the thoracic cavity.

Methylmethacrylate has certain physical properties which indicate its usefulness in vascular surgery. Its highly polished surface does not coagulate blood and it has been used experimentally to replace portions of the thoracic aorta in animals. Various other uses in the fields of general and plastic surgery have been reported. The experimental use of this material in the making of the "lucite calvarium" in monkeys for the observation of the cerebral cortex in living animals has been a significant contribution. This article is not concerned with the uses of such materials outside the body, but their use in various branches of medical practice has been widely reported in the English and American literature.

POLYETHYLENE (POLYTHENE)

In 1936 a process was devised in England whereby ethylene could be polymerized to produce a solid chemically stable product. This compound, called polyethylene, has the most simple structure in which a chain polymer can exist, a chain of 200 to 1000 carbon atoms, each one carrying two hydrogen atoms. It was first produced as an insulating tube for electrical wires, and is reported to have been used in the production of radar equipment and in the insulation of wires in aircraft in which light weight is required. The compound is a tough, flexible plastic which can be produced readily in the form of rods, tubes or film. It is resistant to water and to most other solvents and is chemically inert. Its physical characteristics are unchanged by the extremes of body temperature. It is not opaque to X-rays.

Polyethylene does not depend upon the addition of any plasticizer for its pliability. Manufacturers often add materials known as anti-oxidants to increase its properties of electrical insulation. These forms must be avoided

in obtaining this material for medical and surgical use. In its pure form it does not cause any inflammatory or foreign body response. This has proved true in the brain, thoracic cavity, abdomen, in blood vessels, and in various other body tissues.

Particular attention is necessary in the sterilization of this product since it cannot be autoclaved. Boiling changes the physical characteristics only slightly, but chemical sterilization has proved most satisfactory.

The *clinical and experimental uses* of polyethylene have been greatly extended in the past two years. As a dural substitute it has proved to be useful and dependable, and free of irritation to the surface of the brain. It is well tolerated by bone and when placed in craniectomies will prevent healing of bone for long periods of time—a useful property in the treatment of craniosynostosis. As an aid to intravenous infusion of fluids or blood, particularly in infants over long periods of time, it has proved to be of particular value. The tubing of small calibre can be placed in small veins, and because the tubing shows little tendency to cause clotting the vein can be kept open for several days if necessary. Its use as an adjunct to replacement transfusion in erythroblastosis foetalis is now well known.

In addition, the tubing has been used in common bile duct surgery, in urological surgery as a drainage tube, and in other types of surgery, such as in prolonged ventricular drainage under sterile conditions. The tubing does not collect bile salts or uric acid salts as is common with rubber tubes. Experimentally, polyethylene has been utilized as a vascular prosthesis. Reports of its use in other fields of surgery are gradually accumulating and reference should be made to the recent work of Grindlay (1948) describing a method of fashioning tubes of various types out of polyethylene film which should further extend the use of this material.

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REVISION CORNER

THE USE AND ABUSE OF VASOCONSTRICTORS IN THE NOSE

VASOCONSTRICTORS, properly used, are most useful in the treatment of nasal disorders. Many preparations are available: in 1945 there were on the market in America 240 different vasoconstrictor compounds in the form of sprays, drops, inhalants and ointments. Widely prescribed by the profession, they are often self-prescribed by patients. As new preparations are marketed there is a tendency for the very latest to be tried either by the doctor or by the patient himself, and it is easy to see how their overuse and abuse are bound to occur. The most commonly used vasoconstrictors include adrenaline, ephedrine, neosynephrin, privine and amphetamine. Cocaine of course is also a powerful vasoconstrictor.

NASAL OPERATIONS

To render the field of operation comparatively bloodless, cocaine and adrenaline are usually applied to the nasal mucous membrane before operation: With their proper application the operation may be performed painlessly under the local anæsthesia induced. Should the operation be undertaken under general anæsthesia a similar application will much diminish the amount of bleeding. Sometimes adrenaline in procaine solution or in normal saline is injected with the same object. It is generally recognized that it is safe to inject 7 minims (0.4 ml.) of adrenaline 1:1000 solution, but not more.

EPISTAXIS

Adrenaline solution alone, or mixed with an equal part of cocaine solution (5 or 10 per cent.) applied on wool or ribbon gauze, is often of use in stopping bleeding from the nose. Adrenaline otherwise is not much used in the nose. Following the vasoconstrictor effect there is vasodilatation, the result either of fatigue of the vasoconstrictor mechanism or because the drug contains, in addition, a vasodilator. Most vasoconstrictors have this vasodilating aftermath. The use of adrenaline in the nose often induces an attack of nasal obstruction, watery rhinorrhœa and sneezing, which may last for a few hours or one or two days. Examination of the nose is often helped by spraying it with cocaine solution. The resulting vasoconstriction "opens up" the nose to view. Cocaine should not be used regularly in the nose because of its general effects.

SINUSITIS

The vasoconstrictors are of great value in the treatment of acute sinusitis. It is generally accepted that ephedrine, 0.5 per cent. solution in normal saline, used as drops, or better still in a spray, is the most useful application. Ephedrine is not such a strong vasoconstrictor as adrenaline and no marked after-vasodilatation occurs. The drainage from the infected sinuses is helped by its use, and the cilia of the nasal mucous membrane, upon which drainage largely depends, are not impeded in their work. The ephedrine solution mentioned is also of use in the treatment of acute catarrhal otitis media and Eustachian obstruction; its use helps to re-establish the patency of the Eustachian tube.

In chronic sinusitis the vasoconstrictors may give temporary relief from some symptoms, particularly the headaches of chronic frontal sinusitis; weak ephedrine solutions in normal saline are used in the displacement method of Proetz in the treatment of chronic sinus infections. In most cases of chronic sinusitis, the vasoconstrictors are only of palliative use. They are of no real value, apart from giving very temporary relief of nasal obstruction, in conditions such as deflected nasal septum, hypertrophic rhinitis, nasal polypi and adenoids. They have a certain

usefulness in cutting short attacks of hay fever, and the acute exacerbations of nasal obstruction, sneezing and rhinorrhœa of allergic rhinitis. It is important, however, that they should not be used too regularly for this purpose. Benzedrine is of some use in these cases.

ACUTE RHINITIS (COLDS)

Mild vasoconstriction will give a feeling of relief in the common cold but quite obviously if the inflamed nasal mucosa, with a larger blood supply than normal, is rendered ischæmic for any length of time no real good can result. It may well be that the symptoms of the cold are prolonged if too much use is made of vasoconstrictors. It is likely that a certain amount of sinus infection and ear infection results from the use of the vasoconstrictors in acute nasal infections; there is, however, little doubt that their use is less dangerous than douching, the danger of which can not be over-emphasized.

Some vasoconstrictor preparations contain one of the sulphonamides. It is difficult to see how these can do much good in the short time they spend in passing through the nose; animal experiments have shown that in some cases cilia are destroyed, and that with persistent use a chronic inflammatory change is induced in the mucosa.

Oily preparations containing the vasoconstrictors are less irritating to the nose but they are also less efficient than watery preparations because the "blanket" of mucus covering the mucosa prevents their intimate contact with it. Their use for a long period of time has been shown to produce changes in the lungs (lipoid pneumonia).

"RHINITIS MEDICAMENTOSA"

It will be seen that the vasoconstrictors are of use in some acute conditions, particularly acute sinusitis. Their use regularly for any condition should be condemned. Some patients cannot face the day without spraying or instilling some preparation into their noses. In time they find they have to repeat the process every few hours to get any relief at all. Many will not venture out of their houses without taking with them a handy inhalant. These patients never give their noses a chance to be normal. As time goes on they tend to try different and usually more potent preparations. Some such patients have a nose which is found on examination to resemble that seen in marked allergic rhinitis. The mucosa is swollen, pale and "boggy." Lake of the Mayo Clinic has suggested the name of "rhinitis medicamentosa" for the condition. It has already been mentioned that the phase of vasoconstriction is followed by one of vasodilatation; this appears to affect the deeper venous blood spaces rather than the superficial vessels, hence the mucosa is congested but pale.

Many patients with allergic rhinitis make the condition worse by the prolonged use of vasoconstrictors and so do many sufferers from "catarrh"; so also do some whose noses show definite mechanical obstruction. Most of these patients will be more comfortable if they can be persuaded to stop the regular use of vasoconstrictors. For some days the nose may feel more stuffy than usual but after this the symptom as a rule improves.

A careful examination should be made so that once the abuse of the vasoconstrictor has been corrected, a correct diagnosis can be arrived at and the appropriate treatment carried out. Cases of deflected septum or polypi may require surgical interference. Treatment for sinusitis should be instituted. Many cases may be found to be those of allergic rhinitis for which the variety of possible treatments indicates the difficulty of any one giving a satisfactory result. In America it was estimated that in one week in 1942, 23,000,000 persons suffering from the common cold spent approximately \$11,500,000 on medication. It may safely be said that little real good and not a little harm resulted from all this expenditure and "care" for the common cold.

W. A. MILL, M.S., F.R.C.S.

THE SIGNIFICANCE OF HÆMATURIA

THE common causes of hæmaturia vary to some extent with the age of the patient. An effort should always be made to establish the correct diagnosis, as it is usually a sign of a serious condition.

CAUSAL FACTORS

In a new-born infant hæmaturia, generally slight, may occur as part of the syndrome of *hæmorrhagic disease* caused by a prothrombin deficiency in the blood, which is due to a deficiency of vitamin K; it is associated usually with evidence of hæmorrhage elsewhere in the body. During the first year or so a *meatal ulcer* may be the cause of a little blood in the urine of a male child, especially after circumcision. *Scurvy* is a very rare cause of hæmaturia in children of this country. In a *Wilm's tumour* of the kidney, blood is not often seen in the urine and a lump develops in the loin.

Hæmaturia may occur in *acute nephritis* in the absence of œdema, and this is commonly observed in children, the nephritis being of the so-called focal type and the prognosis good. If the centrifuged deposit of urine contains epithelial and blood casts, that would point to the condition being nephritis. Nephritis continues to be a common cause throughout early adult life, and as it is in most cases accompanied by œdema and casts in the urine it does not often present any difficulty in diagnosis. *Blood diseases*, such as leukæmia and purpura, and occasionally *glandular fever*, may be a cause in childhood as well as in adult life.

In the first half of adult life other causes become common and *tuberculosis*, *calculus* and *papilloma of the bladder* must be considered. Scanty intermittent hæmaturia is seen in about one-fifth of cases of *congenital cystic kidneys*, and as a rule the condition is not recognized before the age of thirty years. It is easy to diagnose when a mass can be felt in both loins, but in *unilateral cystic disease* confusion with a neoplasm may occur and a pyelogram is helpful in differentiating the two conditions. In middle age and old age *hypertension*, *neoplasm* and *prostatic disease* have all to be added to the list of causes of hæmaturia. It is always advisable to make sure that the patient is not having a sulphonamide preparation as this may give rise to hæmaturia, and the same can occur with big doses of dicoumarol or heparin.

DIFFERENTIAL DIAGNOSIS

When the amount of blood is small the appearance of the urine is smoky, and in larger amounts there is a red appearance which can easily be detected. In a urethral condition, such as a caruncle, and in prostatic disease it occurs mainly in the first half of micturition, whereas in bladder lesions, such as a growth or a stone, it is seen in the later part of micturition. In renal conditions, such as nephritis, tuberculosis, calculus or growth, blood is present in the same amount at all stages of micturition. This information will often be volunteered by a male, but a female has not the same opportunity for observing the time at which the blood is passed.

The presence or absence of pain is of help in differentiating the cause of hæmaturia. A calculus in any part of the renal tract usually gives rise to severe renal colic although, of course, a calculus may be present in the complete absence of pain. A painless calculus may be present in paraplegic patients and in those forced to rest for a long time in bed. Acute urethritis and most urethral caruncles will cause pain during micturition and a pyelocystitis may give rise to painful as well as frequent micturition; the presence of much blood in this infection should always suggest the possibility of a stone being the underlying cause. Carcinoma of the prostate gives rise to pain in the perineal area in the majority of cases, but this is not associated with micturition. Malignant growths of the bladder, on the other hand, commonly cause frequency and pain on micturition in the penis and suprapubic area. Sometimes the passing of a blood clot down the renal tract will give rise to severe pain,

and it must not be forgotten that excessive numbers of oxalate crystals in the urine may cause smarting micturition and hæmaturia. A Dietl's crisis is a well-known, though uncommon, cause of pain and of blood in the urine in patients with a movable kidney. On the other hand, hæmaturia is painless when it occurs in an enlarged congested prostate, in papilloma of the bladder and the early stage of malignant disease of the bladder, in renal neoplasms, congenital cystic kidneys and tuberculosis. It is painless in systemic conditions, such as purpura, leukæmia and hypertension, unless the passage of a clot causes pain.

Some information may be gained by inquiring into the act of micturition: in the case of carcinoma of the prostate or an enlarged prostate, frequency and difficulty of micturition occur sooner or later—the stream lacks force and dribbling occurs.

A full clinical examination of the patient, which must always be done, may disclose a general condition, such as purpura, or a tumour or tenderness in the loin may be found. A rectal examination will give evidence of prostatic disease or a large carcinoma of the cervix may be felt involving the ureters and bladder, as this can be a cause of hæmaturia and of uræmia. Hæmaturia may occur in cases of essential hypertension, more particularly malignant hypertension, and the finding of papill-œdema would be diagnostic of the latter.

UROLOGICAL EXAMINATION

The next investigation should be the examination of a specimen of urine microscopically. In a female this should be collected immediately after a bath. If pus is found, then a mid-stream specimen in a male and a catheter specimen in a female should be examined for pus, tubercle bacilli, and cultured. The microscopic presence of red blood cells can be confirmed and hæmoglobinuria ruled out. If pus is present and the culture is sterile it is highly probable that it will prove to be a tuberculous condition and microscopic examinations for tubercle bacilli may prove positive, but if not, special cultures on Lowenstein's media and guinea-pig inoculations should be carried out. If pus is present and *B. coli* or *proteus* is cultured, the diagnosis of an ordinary pyelocystitis is very probable; there may still be an underlying stone, or even a tuberculous infection, but the latter is much more uncommon. As mentioned above, the presence of much blood in a *B. coli* or *proteus* pyelocystitis should suggest the possibility of a calculus.

A renal calculus is probably the most common cause of pus and blood in a non-sterile urine, even when there has been no history of renal colic. In all cases in which the diagnosis cannot be settled by ordinary clinical examination and microscopic examination and culture of the urine, an *X-ray of the renal tract* and an intravenous pyelogram must be carried out. If this proves to be negative a cystoscopy should be done, as this may indicate that the prostate is the cause of the hæmaturia, or it may show a papilloma or carcinoma of the bladder, and by observing the excretion of indigo-carmin from the ureters, after an intravenous injection, a diseased kidney may be recognized. Finally, a retrograde pyelogram may have to be done to exclude with certainty a renal carcinoma, and then only, if this too proves to be negative, should the so-called "essential hæmaturia" be considered as the cause of the condition. The fact that the patient has a high blood pressure should not be regarded as ruling out a renal neoplasm.

There are, of course, other interesting causes of hæmaturia which I have not mentioned. In parts of Africa, for example, the common cause of hæmaturia is schistosomiasis, and the fact that a very characteristic egg can be seen on microscopic examination of the urine made this condition of especial interest to Medical Officers serving in West Africa in the late war.

CHARLES S. D. DON, M.D., F.R.C.P.

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treatment of disseminated sclerosis. Is the physiotherapy part of the treatment of more importance than the prostigmin, which has unpleasant after-effects by causing diarrhoea?

REPLY.—This treatment is not regarded by its author as having any direct curative effect upon the plaques present in the nervous system. It is designed to take advantage of the fact that prostigmin has the property of producing some relaxation of spastic muscles, and of lessening fatigue. Thus it facilitates the use of intensive physiotherapy in the re-education of weak and ataxic limbs. Undoubtedly the physiotherapy is the important, and indeed the fundamental, part of the treatment. Neostigmine methyl sulphate, 1 to 3 mg., is administered daily by injection, together with 15 to 30 mg. by mouth. Side-effects, such as diarrhoea, are avoided by giving the drug after meals and by administration of atropine, 1/200 of a grain (0.32 mg.) or more, daily. The original paper describing the treatment appeared in the *Permanente Foundation Medical Bulletin*, March, 1947, 5, 1.

DAVID KENDALL, D.M., M.R.C.P.

Hay Fever Following Childbirth

QUERY.—My wife, aged twenty-eight, has recently acquired a most intractable hay fever, which is distressing her not a little. Her history is as follows:—In August last she gave birth at full term to a normal male child, following a pregnancy that was marked by the sudden appearance of the hay fever in the second month. Apart from this complaint, the pregnancy was normal. She has never before had any sign of allergic complaint. She has previously had two normal pregnancies without any sign of hay fever, and her medical history contains nothing of note. Two thorough E.N.T. overhauls during the pregnancy revealed nothing abnormal. Some very transitory relief was afforded by antihisan tablets and antistin-privine in a nasal spray. A short stay in London during the pregnancy also helped, but the symptoms recurred on return to Cornwall. She is at present breast feeding the child, and is becoming rather depressed by the hay fever. The problems are: (a) How to relieve the present attack? (b) Would benadryl abort the attacks of hay fever, or would this drug have a deleterious effect on the child and therefore be contra-indicated? (c) What are the prospects of the hay fever disappearing when the child is weaned? (d) Would it be advisable to wean the child at this stage? It is regretted that a change of locality is not at present feasible, for domestic reasons.

REPLY.—The condition described, since it first appeared apparently in January, is not hay

fever or pollinosis, but a vasomotor rhinitis. Nothing is mentioned as to whether there is any family history of any allergic condition. It is not uncommon to find allergic symptoms appearing in a person during pregnancy and no entirely satisfactory explanation has been offered. In most cases the pregnancy has uncovered a previously latent inherited sensitivity and the first step should be to have the patient's skin tested by a competent allergist. Should such sensitivities be found, removal of the offending allergens from the environment as much as possible and desensitization offer the best chances for relief. In the meantime, antihistamine drugs by mouth and the use of antistin-privine drops in the nose are indicated. These drops should be used very sparingly. Antihistamines afford temporary relief and all three at present available should be tried, i.e. antihisan, antistin, and benadryl. The initial dose in this particular case should be 50 mg. of the first two and 25 mg. of the last, four-hourly if required, and the dose may be increased gradually to four times this amount four-hourly. The drug finally chosen should be that which gives the most relief with the least side-effects. No serious deleterious effect in the child should be expected, but the side-effects found in the adult may occur and so the drugs must be used cautiously in the manner described. The chances of the condition disappearing spontaneously at weaning are not great and should not be expected, and there is no indication for weaning the child.

C. J. C. BRITTON, M.D.

Intercurrent Infections in Malarial Patients

QUERY (from Ceylon).—I have recently had a patient with chronic malaria who developed a high fever due to influenza. It is usually said that when a malarial patient develops some other infection, this results in a recrudescence of the malaria. In this patient I was unable to find any malarial parasites in the blood during the pyrexia. The patient was not given anti-malarial drugs before the blood film was made. Could you tell me whether this is a usual experience? I should also like to know what treatment should be given to such a patient.

REPLY.—The patient referred to must have developed and maintained a trophozoite immunity to his own particular strain, sufficient to enable him to hold the parasites in check in spite of the complication of an added influenza attack. A malaria relapse is not necessarily provoked by the development of some other disease; it depends upon the measure of the

NOTES AND QUERIES

Auriculo-Ventricular Nodal Rhythm

QURRY.—In the November issue of *The Practitioner*, in the article on the "Newer Inhalation Anaesthetics" (p. 363) it is stated with reference to cyclopropane: "Electrocardiographic tracings have frequently shown that the regular heart beat in deep cyclopropane anaesthesia is an auriculo-ventricular nodal rhythm. The serious import attributed to nodal rhythm by cardiologists justifies abandonment of the production of deep anaesthesia with cyclopropane alone." On looking up A.V. nodal rhythm, I am unable to find any cardiologist who attributes to that condition the serious import that Dr. Hellijas and Dr. Tovell assert. In fact Price, on page 929 of his "Textbook of Medicine", says: "The condition is of no clinical importance"; whilst Paul White, in "Heart Disease", page 925, states: "... the A.V. nodal rhythm ... appears to be a harmless condition, not needing treatment in itself and not easily controlled by any special therapy". I should be grateful if you could make the position clear and state how serious a condition, or not, A.V. nodal rhythm is.

REPLY.—We wish to emphasize the need for caution in comparing the action of the heart in the unanaesthetized individual with the action of the heart in the patient anaesthetized, in this instance, by cyclopropane. This agent has a potent parasympathomimetic effect. References to the effect on vagal tone and to the increase in irritability of the cardiac musculature and conducting mechanism produced by cyclopropane were included in the original article under discussion. We quote further now from White (1941):—

"A-V nodal rhythm may be due to marked depression of the normal pacemaker of the heart situated in the sino-auricular node and failure of any other part of the auricular muscle to assume its rôle ... occasionally unusual irritation or irritability of the functional tissues accounts for premature beats or paroxysmal tachycardia of A-V nodal origin ..."

Graybiel and White (1941) also state: "It is due to the escape of the A-V node, which then controls the action of both auricles and ventricles, either as the result of depression

or as the result of irritability of the A-V node ... control, paroxysmally or otherwise, of the beating of the whole heart". The more serious abnormalities of cardiac rate and rhythm occur in the presence of high concentrations of cyclopropane, at or near the level of respiratory arrest. Willius (1930) states that A-V nodal rhythm "is a constant finding when death is taking place and uniformly it ushers in the onset of marked ... sudden ... of nodal rhythm ... Cerebral ... both, have been produced experimentally and graphic transitions have appeared which are similar to those that have been produced by the dying human heart."

In a recent publication, Ziegler (1948) analysed the electrocardiographic changes occurring

during the performance of the Blalock-Taussig procedure on 175 children, consecutively. The principal anaesthetic agent employed was cyclopropane (with oxygen), with admixture of small amounts of ether; in certain patients, the mixture was changed to ether and oxygen, or oxygen alone. The ectopic arrhythmias observed arose either from depression of the sinus pacemaker or from increased irritability of another portion of the heart.

Depression of the S-A node occurred in more than half of the children exhibiting abnormal rhythms; in all instances this produced a form of A-V nodal rhythm. In 52.3 per cent. of the patients with A-V nodal rhythm there was spontaneous reversion to normal sinus rhythm; in 21.6 per cent., the administration of atropine caused a reversion to S-A rhythm; atropine produced little effect in 9.1 per cent.; in 17 per cent. no classification on the basis of response to atropine could be made. Atropine produced a reversion to S-A rhythm when a slow A-V rhythm existed; in the presence of rapid nodal rhythm, atropine apparently had no effect.

The mechanism of cardiac action was observed in seven children who died at some point during anaesthesia or operation. Bradycardia, of either sinus or A-V nodal origin, occurred in each instance pre-terminally. In five, the bradycardia either recurred after the administration of atropine or was not affected by it. "It therefore seems evident that bradycardia, either sinus or nodal, with a rate of less than 50 per minute, and with failure to respond to the administration of atropine, constitutes a specific warning of impending terminal asystole."

Recent clinical opinion would indicate that the occurrence of irregularities of cardiac rate or rhythm during anaesthesia and operation should not be regarded lightly. "With these principles in mind ... the pharmacological properties of cyclopropane involved in the regulation of cardiac action; the tendency for the more serious arrhythmias produced by this agent to occur at or near the level of respiratory arrest; the demonstration that the slow pulse appearing in the presence of high concentrations of cyclopropane is frequently an A-V nodal rhythm; the observation that A-V nodal rhythm is a common precursor of terminal asystole in both the anaesthetized and unanaesthetized state ... the appearance of any arrhythmia or marked alteration in cardiac rate (such as A-V nodal rhythm) during the administration of cyclopropane, should be regarded as a significant indication of the need for remedial measures."

CARL S. HELLIJAS, M.D.

R. M. TOVELL, M.D.

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Prostigmin in Disseminated Sclerosis

QUERY.—I should be grateful for an explanation of the action of prostigmin in Dr. Kabat's

PRACTICAL NOTES

Inhalation of Isopropyl-nor-Adrenaline Dust in Asthma

THE inhalation of penicillin as a dust has been recommended for various reasons, including simplicity of equipment and administration, maximum concentration of drug per unit area within the respiratory tract and slow absorption into the systemic circulation. L. R. Krasno and his colleagues (*Science*, October 29, 1948, 108, 476) have now used this method with isopropyl-nor-adrenaline in 24 patients with asthma. The preparation of the drug employed was an American one named "norisodrine", and full details are given of the apparatus used. In six normal subjects who inhaled the amount of dust (3 to 5 mg.) released during one normal respiration, no effect on the pulse or blood pressure was noted, and there were no untoward symptoms. The asthmatic patients were instructed to take one whiff of the norisodrine dust during an impending attack of asthma, and again within $\frac{1}{2}$ to 1 hour if necessary. Sixteen of the asthmatic patients were controlled by norisodrine dust alone, whilst the other eight required, in addition, either aminophylline and iodides and/or an antihistamine. In none of this latter group was the asthma controlled by any of these other drugs alone. Four of the asthmatic patients complained of dizziness and/or palpitations following the use of norisodrine dust. One patient took as much as 100 mg. of norisodrine daily without untoward effects. No evidence of resistance to the drug was noted, although these patients had been taking it for ten months. On the basis of these results it is claimed that "this drug has a definite place in the symptomatic treatment of asthmatic diseases. It should be useful in many instances of bronchospasms of a non-asthmatic origin. It can apparently be inhaled in dust form with a wide margin of safety".

p-Aminosalicylic Acid in Tuberculosis

THE use of *p*-aminosalicylic acid, alone and in combination with streptomycin, in a series of cases of tuberculosis is recorded by H. Steinlin and W. Wilhelm (*Schweizerische Medizinische Wochenschrift*, December 18, 1948, 78, 1219). The drug employed was the synthetic preparation "aminacyl" (Wander), and was first administered in the form of a 20 per cent. solution of the sodium salt, but owing to the bitter taste dragées of 0.34 g. were substituted, 10 dragées four times daily, i.e., a total daily dose of 12 g. free *p*-aminosalicylic acid for four consecutive days, followed by an interval of three days. In

cases of tuberculosis of the kidney the total daily dosage was reduced to 6.9 g., and the treatment was carried out continuously for six to eight weeks before a pause of eight to fourteen days. The patients were divided into groups: In the first (24) aminacyl alone was given by mouth, resulting in a decrease in temperature in 15 of 17 with fever before treatment; a decrease in blood sedimentation rate in 14 of 20 patients in whom it was previously raised; increase in haemoglobin in 19; decreased expectoration in 10; 12 of 17 patients with positive sputum were negative after treatment; 17 of the 24 showed increase in weight, and the general condition was improved in 18 patients. The duration of treatment ranged from two to seven months. The second group consisted of 26 patients who were given combined *p*-aminosalicylic acid and streptomycin therapy, receiving 0.5 g. streptomycin twice daily up to a total dosage of 100 g. Of these patients, 8 showed decrease in temperature; 16 lowered blood sedimentation; 18 increased haemoglobin; 13 decrease in expectoration; 17 negative sputum; 15 increase in weight; 18 improvement in general condition. The treatment in this group also was from two to seven months. The third group (53) received local *p*-aminosalicylic acid therapy, and in 16 cases oral administration also. A 20 per cent. solution diluted with saline or distilled water to 10 or 5 per cent., or lower, was employed by injection or instillation. Of 47 empyemas positive before treatment, 26 were negative after one to five months. Cavities and fistulae also responded well to local treatment.

Veratrum Viride in Essential Hypertension

FORTY patients with essential hypertension have been treated with *veratrum viride* at the Massachusetts Memorial Hospital (E. D. Freis, and J. R. Stanton: *American Heart Journal*, November 1948, 36, 723). The preparation used was the whole powdered mixture of alkaloids prepared in tablets, and the dosage varied from 10 to 40 Craw units in twelve hours. There was considerable individual variation in the size of the effective dose in the treated series, the effective dosage being based on a reduction of at least 20 mm. in systolic and 15 mm. in diastolic pressure. It was found that if the effective dose was more than 10 Craw units, ingestion of the total dose at one time often resulted in side-reactions. In order to prevent such reactions to cumulative overdosage, the drug was given at dosage intervals of twelve

subject's trophozoite immunity. Treatment depends upon circumstances. If the patient has recently suffered from serious and easily provoked relapses, and the new infection is likely to run a prolonged or severe course, it would be wise to give antimalaria treatment, but in the smallest dose, with the maximum interval, which proves sufficient to keep the blood free from trophozoites. For example, a case of severe typhoid, mistaken at the beginning for the typhoid-like form of falciparum malaria, and treated vigorously as malaria for the first ten days or so, is likely to give the physician much added anxiety later on; so that over-treatment of the malaria element in a double infection may aggravate the complicating disease. On the other hand, if a malaria subject is to undergo a major surgical operation, he should be given a short course of treatment beforehand, if there is time, and continued after the operation in a dosage sufficient to keep his infection under control. A relapse accompanied by violent vomiting might be disastrous.

LIEUT.-GENERAL SIR WILLIAM MACARTHUR,
K.C.B., D.S.O., M.D., F.R.C.P.

Epidemic Pleurodynia

QUERY.—A recent local "epidemic" of a peculiar condition in children suggests Bornholm's disease, but I cannot obtain any positive proof of this. Are there any signs or symptoms which are pathognomonic? Is there any special seasonal incidence? Are there any laboratory investigations which are of real value?

REPLY.—Most of the epidemics described have occurred in the late summer and autumn, and children under fifteen are mainly involved. Sudden onset of spasmodic pain along the insertion of the diaphragm; shallow, rapid respiration with fever lasting for twenty-four hours, and a marked tendency to relapse are the characteristic features reported, with absence of physical or radiological signs of involvement of a serous membrane. There are no laboratory investigations of positive value in diagnosis, although an eosinophilia has been observed during convalescence in some instances.

A. E. GOW, M.D., F.R.C.P.

Maternal Rubella and the Deaf Child

Miss Sylvian M. Martin (Licentiate of the College of Speech Therapists) writes:—

I have read the article on "The Management of Deafness" in the December issue of *The Practitioner* (p. 469) and am sending you

the results of a small investigation on maternal rubella and resultant deafness in the child which may prove of interest. A questionnaire was sent to my past and present patients and to the parents of children in deaf schools who were willing to cooperate, and the following figures were obtained:—

	Boys	Girls	Total
Deaf children born 1940-41 ..	64	38	102
History of rubella during first four months of pregnancy ..	16	20	36

Rubella was suspected in a further 6 cases but had not been diagnosed. It was not possible to obtain full details of all the children, but in several cases there were concomitant defects of eyes or heart, or both. A few of the children were mentally defective but the majority had average or above average intelligence. Left-handedness or ambidexterity was present in 40 children, and in 16 of these there was a familial history of left-handedness. 15 children were right-handed but had left-handedness in the family. Nearly all the children were small, very fat and of somewhat fragile appearance, and could well be taken for members of one family. The birth weight in 15 was between 5 and 6½ lb., in 2 it was 7½ lb., and in 2 the weights were 3½ lb. and 4½ lb. respectively.

As regards the reference in the article to the training of parents of deaf children in the Tracey Clinic in Los Angeles, and the superiority of these children in the comprehension of language and so forth when starting school, it may be of interest to readers to know that parents of children attending deaf clinics at two London hospitals (the Westminster Children's Hospital, and the Metropolitan Ear, Nose and Throat Hospital) are given instruction in the development of speech, lipreading, and the like, in their children. The mothers attend the clinic and watch the methods used, and there are also quarterly parents' meetings for the discussion of problems, when advice is given by doctors, psychologists, and the parents of older children who have had experience in such problems. Occasional parents' classes are also held, at which I demonstrate with the children and lecture on speech, lipreading and general training. The superiority of such children is indisputable: some can read and write from dictation at the age of four or five years, and can lipread simple conversation and stories even before their speech is very intelligible or fluent. In some instances, where deaf day schools are not available, the children are attending ordinary schools and are keeping up with hearing children of their own age in many subjects: in a few subjects they are below standard, but all the children are mostly well ahead of the hearing child in reading and writing. In all cases residual hearing is stimulated and trained, and hearing aids are supplied when it is felt that they will be helpful.

tion of 100 samples of urine were positive in all but four cases, three hours after injection. In 11 cases positive readings were obtained at the end of one hour after injection, and in one case forty-five minutes after the toad was injected. This last case is stated to be unusual, and the author states: "Injection of 10 ml. of patient's untreated urine can give a positive result in 2-4 hours, indicated by the presence of masses of spermatozoa in the toad's urine". The test was also found of value in the study of abortion.

Treatment of Pityriasis Versicolor and Gibert's Pityriasis Rosea

In a note on the diagnosis and treatment of pityriasis versicolor and Gibert's pityriasis, Y. Pécher (*Presse Médicale*, November 3, 1948, 56, suppl., 776 C) recommends for pityriasis versicolor: (1) change of linen after each application of medicament and prompt laundering of the linen discarded; (2) avoidance of wool next to the skin; (3) energetic friction for ten minutes with soft potassium soap, followed by a mild sulphur bath. The following formulæ are recommended for local application:

Iodine	} $\bar{a}\bar{a}$ 2 g.
Salicylic acid	
Alcohol 9 per cent.	to 100 ml.
For delicate skins:—	
Benzoic acid	4 g.
Salicylic acid	2 g.
Adeps	24 g.

Healing is usually rapid, but in order to prevent recurrences, rigorous body hygiene is necessary. In those cases in which perspiration is abundant, friction with spirit of camphor followed by the following application is advocated:—

Glycerin 30 per cent.	
Tannin	$\bar{a}\bar{a}$ 40 g.
Pityriasis rosea (Gibert) heals as a rule spontaneously, and is not troublesome. In general, indigestible foods should be avoided and also stimulating nerve tonics. Moderation in the use of bathing and soaps is essential, especially in the pruritic forms. A spirit or almond oil lotion may be applied and in pruritic cases a bland powder, but no ointments or irritating lotions. As a rule no medical application is necessary, but a weak ichthylol application may be used:—	
Ichthylol	1 g.
Talc	} $\bar{a}\bar{a}$ 10 g.
Zinc oxide	
Glycerin 30 per cent.	
Lime water	

To be made up in the form of a cream or water paste—never as an ointment

"Antabuse" in the Treatment of Alcoholism

A REPORT on six months' experience in the treatment of cases of chronic alcoholism with the sensitizing drug "antabuse" (tetraethylthiuramdisulphide) is given by O. Martensen-Larsen (*Lancet*, December 25, 1948, ii, 1004). A series of 83 patients received treatment, the general method adopted being as follows:—After physical examination, and study of the medical psychiatric and social background, the patient was given 1 to 1.5 g. antabuse and told to continue with 0.5 g. daily. The patient was also told that he would become ill if he drank alcohol, and was asked to return for a second interview two to three days later. The patient takes two or three drinks either the night before or immediately before the second interview, in order to assess the effect of treatment. Sometimes he will have already taken alcohol, and in larger amounts, before this time, and with a violent reaction, which is of benefit from the therapeutic point of view. Some patients, if heavy drinkers, can take considerable amounts of alcohol before a reaction. In these cases the treatment is continued and the patient tested at intervals of four to six days. Of the treated cases, 32 benefited sufficiently from the treatment to continue on token dosage (0.0625 g. daily) after a few weeks' observation, after which treatment was controlled by telephone; 29 see the doctor at regular intervals, when further dosage is fixed, which must be sufficient to prevent the taking of more than one or two drinks at a time; 13 were difficult cases from the psychoneurotic point of view, have been helped to some degree, but need long observation before definite conclusions can be drawn; 9 cases failed to respond to treatment. In conclusion it is stated that "further observation is required for complete assessment of the results".

Application for Unbroken Chilblains

The formula for a collodion for the treatment of unbroken chilblains is given by I. R. H. Miller (*Chiropodist*, December 1948, 3, 308):—

Strong tincture of iodine ..	120 minims (7 ml.)
Compound tincture of benzoin ..	120 minims (7 ml.)
Menthol cry. stals ..	5 grains (0.32 g.)
Flexible collodion ..	to 1 ounce (28.4 ml.)
To be applied to affected areas three to five times weekly until itching has ceased.	

The preparation is stated to be an excellent stimulant and protective, not displeasing in colour or odour, to dry well, and to have good keeping properties in bulk.

hours, the dose being further subdivided so that not more than 10 Craw units were ingested per hour. When the drug was administered by the oral route the hypotensive effect began to appear at the end of one to two hours, reached a maximum in four to six hours, and largely disappeared at the end of fourteen hours. The treatment was found to be useful in cases of hypertensive crisis, in severe long-standing hypertensive disease resistant to other forms of treatment, and in hypertension complicated by cardiac failure. In some cases continued treatment resulted in "diminution in the cardiac size and reversal of electrocardiographic changes toward normal". No deaths and no toxic reactions causing more than transient disability occurred, but it is stated that "the development of side-effects and of changing sensitivity to a given dose were sufficiently frequent to limit its usefulness in the treatment of patients with mild or moderate degrees of hypertension".

Dangers of X-Ray Epilation

THE dangers of removal of superfluous hair by X-rays are emphasized by D. E. H. Cleveland (*Canadian Medical Association Journal*, October 1948, 59, 374), who gives detailed particulars of four cases, one necessitating amputation and one terminating fatally. In each case radiodermatitis followed by the development of squamous-cell carcinoma occurred. The patients, all of whom had been treated at commercial institutions, were seen from ten to seventeen years after receiving treatment. Other cases, however, were seen in the earlier stages and exhibited dryness of the skin with varying degrees of erythema, early atrophy and telangiectasia on the cheeks, chin, nose and neck.

In the fatal case recorded the woman had been treated for superfluous hair on the forearms, and symptoms of radiodermatitis on the forearms and breast appeared seven years after treatment. A year later an ulcer appeared on the lower part of the left breast, and when seen eight years later the whole lower half of the breast and the chest wall immediately below was occupied by a deep ulcer crater which proved to be squamous-cell carcinoma. There was extensive metastasis, and death occurred four months later—eighteen years after being treated by X-rays.

In the summary to his article the author states: "The view that permanent removal of superfluous hair by radiation therapy cannot be accomplished without permanent skin injury is strongly supported".

Treatment of Angina Pectoris

FURTHER confirmation of the value of nitroglycerin in the treatment of angina pectoris is forthcoming from Sweden. Using as his experimental material a patient in whom the pain of angina pectoris was regularly produced by two minutes of the test exercise, and checking the results by electrocardiography, E. Nyman (*Acta*

Medica Scandinavica, October 1948, 131, 563) found that 0.5 mg. of nitroglycerin by mouth increased the amount of exercise necessary to evoke pain from two to four minutes. Theophylline ethylenediamine, in oral doses of 0.2 g. thrice daily for three days, increased the time from 1½ to 3 minutes, whilst the same preparation intravenously in doses of 0.24 g. given fifteen minutes before the test, increased the time from two to four minutes. Papaverine hydrochloride intravenously had no effect upon the amount of exercise required to produce pain. Slow-acting drugs were found to have little effect. Attention is drawn to the fact that the daily dosage of theophylline ethylenediamine necessary to give relief, if taken by mouth, is sometimes apt to produce toxic reactions if maintained for any length of time.

Pregnancy Tests Using Male Toads

IN 1947 appeared the first report on a new pregnancy test in which male toads (*Bufo arenarum* Hensel) were used as reacting animals, and the author, C. Galli-Mainini, now summarizes the accumulated statistics for the intervening year (*Journal of the American Medical Association*, September 11, 1948, 138, 121). The test, which is simple, is as follows:—

Within a few hours of subcutaneous injection of 10 ml. of urine from a woman in whom pregnancy is suspected, a drop of the injected male toad's urine is collected by means of a pipette and examined microscopically. The positivity or negativity of the reaction to the test is the presence or absence in the toad's urine of spermatozoa produced in the testicle as a direct result of gonadotrophic stimulation.

Of 1,422 cases of suspected pregnancy tested by the author, in 960 instances the patients were not pregnant and negative results were obtained in all. Of 462 cases of verified pregnancy positive results were obtained in 458. Thus in the total of 1,422 tests there was an accuracy rate of 99.72 per cent. Accumulated data show 98 to 100 per cent. correct results in pregnancy tests in 2,661 cases, and 100 per cent. exact negative response in 1,166 cases in which control tests were made with urine from non-pregnant women. The advantages claimed for the test are: (1) its specificity; (2) the speed of the reaction, results being obtained within three hours of injection of the urine; (3) the simplicity of the technique. As regards the last point it is stated that no special preparation of the urine to be injected is needed, the injection is without difficulty, as also collection of the toad's urine, and the microscopic observation is immediate, the differentiation of the spermatozoa being simple because of their number and well-defined characteristics.

A further report on the use of the male toad test is given by M. Haines (*Lancet*, December 11, 1948, ii, 923). Results obtained from injection

mechanism of cardiac disorders", Dr. Luisada has attempted to deal with clinical cardiology as a functional problem. Although some of his views may not receive universal acceptance, the approach is a sound one, and the book should prove a useful introduction to cardiology for the student coming straight from physiology. Its value is considerably enhanced by a profuse supply of excellent diagrams: these alone will commend it to the clinical teacher.

An Elementary Atlas of Cardiography.

By H. WALLACE-JONES, M.D., M.Sc., F.R.C.P., E. NOBLE CHAMBERLAIN, M.D., M.Sc., F.R.C.P., and E. L. RUBIN, M.D., M.I.R.E. Bristol: John Wright & Sons, 1948. Pp. 108. Figures 99. Price 12s. 6d.

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Krebsmetastasen. By HANS E. WALTHER, M.D. Basle: Benno Schwabe & Co., 1948. Pp. 560. Illustrated. Price Sw. frs. 60.

THIS is a very unusual and welcome book. It is beautifully produced; its diagrams, numerous tables, photomicrographs and X-ray plates are clear and well chosen. Its purpose is to describe metastases, and the work is based on the material available at the Pathological Institute in Zürich. Apparently the author, a radiologist, was stimulated to the investigation by the frequency with which he met metastases in patients in whom there was no obvious primary. The result is a well-documented, anatomical, pathological and, to a less extent, radiological investigation of the whole problem of the formation of metastases. This has involved a description of the lymph channels and nodes and also general considerations of the circulation. In general it is maintained that the distribution of metastases follows the normal course of lymph drainage or direction of the circulation. The metastatic spread by the circulation is divided into four general types: the first being one in which the origin is in the lung itself; the second in which

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REVIEWS OF BOOKS

Textbook of the Rheumatic Diseases. EDITED BY W. S. C. Copeman, O.B.E., M.D., F.R.C.P. Edinburgh: E. & S. Livingstone Ltd., 1948. Pp. viii and 612. Figures 289. Price 50s.

THIS is an authoritative and clearly written textbook which includes up-to-date information on every aspect of the rheumatic diseases. It is outstanding for the complete way in which it covers the subject, and for the masterly reproduction of the numerous skiagrams which illustrate the text throughout. A selection of chapter headings will convey some idea of the extent of the information given. These include an Historical Survey (W. S. C. Copeman); The Anatomy and Physiology of Pain; The Clinical Approach to Pain (J. H. Kellgren); Climatic and Environmental Factors in the Rheumatic Diseases (L. G. C. E. Pugh); Special Pathology of the Rheumatic Diseases; Clinical Pathology of the Rheumatic Diseases (Campbell Golding); Physiotherapy in the Treatment of the Chronic Rheumatic Diseases (H. Burt); Psychiatric aspects of the Rheumatic Diseases (W. Tegner and Henry Wilson); Statistics of the Rheumatic Diseases (Percy Stocks). In addition to these there are chapters on acute rheumatism, gout, rheumatoid arthritis and sciatica, by a team of distinguished contributors. In reading this book it is impossible not to be struck by the fact that although advances have been made, notably in the interpretation of pain, in the recognition of the disc syndrome, and in the use of physiotherapy, the hard core of the rheumatic diseases remains untouched. This is more obvious to-day than it was fifteen years ago, because of the rapid and revolutionary advances that have been made in other fields. In a group of diseases in which theory commonly outstrips the known facts and uncontrolled therapeutic measures spring up like mushrooms, the sound judgment shown throughout this publication must be appreciated. This is not a book for experts, but most experts in the rheumatic diseases will wish to possess it. For the practitioner who wants to take an intelligent interest in his rheumatic patients it will be valuable.

Clinical Endocrinology. By LAWRENCE MARTIN, M.D., F.R.C.P., and MARTIN HYNES, M.D., M.R.C.P. London: J. & A. Churchill Ltd., 1948. Pp. viii and 222. Figures 33. Price 15s.

THIS short book succeeds in giving a readable and reasonably complete summary of the

position that endocrinology now holds in the design of general medicine. This considerable feat has been achieved by a critical selection of the literature on which the text is based, and by the admirable avoidance of repetition by using a system of cross-references. One sufficiently detailed and practical account of the methods of using adrenal cortical extract and D.O.C.A., for instance, serves both for the section on the treatment of Addison's disease and for that dealing with Simmonds's disease. The chapter on disorders of the thyroid gland is probably the best in the book, and gives an account of the place of thiouracil in the treatment of thyrotoxicosis that will be accepted at the present time by most people who understand the problem. This is a balanced and useful book that will be welcomed by both undergraduate and postgraduate students.

Modern Methods of Infant Management. EDITED BY W. R. F. Collis, M.D., F.R.C.P., F.R.C.P.I. London: Wm. Heinemann (Medical Books) Ltd., 1948. Pp. vii and 285. Figures 63. Price 17s. 6d.

THIS pocket book by Dr. Collis, paediatrician to the Rotunda Hospital, Dublin, written in collaboration with an obstetrical, a paediatric, and a nursing colleague, is a useful elementary book on infant management "before, during and after birth" to the end of the first year. The wealth of practical detail will commend it to midwives and nurses for whom it is primarily intended. Medical students and practitioners will find, despite several misstatements of fact and a few unorthodox views, a fair and lucid outline of current paediatric practice. The author has rightly extolled the virtues of breast feeding, but might have given a fuller account of its physiology and the management of the numerous complications which are so common in the early weeks.

Heart. By ALDO A. LUISADA, M.D. Baltimore: The Williams & Wilkins Co.; London: Baillière, Tindall and Cox, 1948. Pp. xi and 653. Figures 352. Price 55s.

THE subtitle of this book, "a physiologic and clinical study of cardio-vascular diseases", gives an idea of the author's approach to the subject. It is a refreshing attitude to cardiology, especially in comparison with the stereotyped textbook of cardiology. Described by Dr. H. L. Blumgart in his foreword, as "a brilliant investigator in the pathologic physiological

mechanism of cardiac disorders", Dr. Luisada has attempted to deal with clinical cardiology as a functional problem. Although some of his views may not receive universal acceptance, the approach is a sound one, and the book should prove a useful introduction to cardiology for the student coming straight from physiology. Its value is considerably enhanced by a profuse supply of excellent diagrams: these alone will commend it to the clinical teacher.

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NOTES AND PREPARATIONS

NEW PREPARATIONS

D.F.P.-BOOTS is di-isopropyl fluorophosphonate, one of the most active of the alkyl fluorophosphonates, which possesses a strong anticholinesterase action. Its use is indicated in the treatment of glaucoma, paralytic ileus, and myasthenia gravis. Available in 2 ml. ampoules and in the form of eye-drops. (Boots Pure Drug Co., Ltd., Station Street, Nottingham.)

DUOMYCIN (aureomycin hydrochloride: Lederle), a potent antibiotic against many gram-negative and gram-positive organisms and indicated in infections resistant to penicillin, streptomycin or the sulphonamides, is so far not available for general use in this country. Manufacture in the Lederle Laboratories is, however, being rapidly extended with a view to increased availability in the near future. (Cyanamid Products Ltd., Brettenham House, Lancaster Place, London, W.C.2.)

KINA-'REDOXON' tablets each contain 30 mg. of redoxon ascorbic acid and 30 mg. of quinine sulphate. They have been prepared for the prophylaxis and treatment of the common cold and influenzal conditions. Issued in bottles of 50 and 500 sugar-coated tablets. (Roche Products Ltd., Welwyn Garden City, Herts.)

PROCAINE PENICILLIN A & H, a true salt formed by combining procaine and penicillin G in equimolecular proportions, has been prepared for intramuscular injection in the form of a suspension in arachis oil, with 2 per cent. aluminium stearate added as a dispersant to ensure uniformity of dosage and prolonged penicillin action. It is issued in rubber-capped vials of 10 ml., each ml. containing 300,000 units of penicillin and the equivalent of 120 mg. procaine base. (Allen & Hanburys Ltd., Bethnal Green, London, E.2.)

VIOFORM CREAM AND OINTMENT contain 3 per cent. iodochlorhydroxyquinoline, the former in a drying, water-miscible base, the latter in a greasy ointment base. Their use is indicated in sycosis barbae, seborrhoeic and other forms of dermatitis, eczematous eruptions, psoriasis, pruritus and other skin affections. Available in containers of 1 oz. and 1 lb. (Ciba Laboratories Ltd., Horsham, Sussex.) Other preparations recently placed on the market by this firm are **ESDRONE**, a mercurial diuretic combined with theophylline; **PYRIBENZAMINE**, an antihistamine drug for the treatment of allergic conditions; and **PRISCOL**, a vasodilator drug derived from imidazoline.

APPLE JUICE

ONE of the only fresh, unadulterated fruit drinks available in this country, Shloer Liquid Apples, formerly imported from Switzerland, is now

manufactured in Gloucestershire. Samples will be supplied to doctors on application. (Sole distributors: E. I. Michel & Co., Ltd., 415/7 Oxford Street, London, W.1.)

NEW APPARATUS

POLYTHENE CANNULÆ are now included in the accessories available for use with Sterivac transfusion equipment and are issued in four sizes, numbers 1, 2, 3, 4, having an internal diameter of 0.5 mm., 1.0 mm., 1.5 mm., and 2.0 mm. respectively. (Allen & Hanburys Ltd., Bethnal Green, London, E.2.)

THE SPARKLETS AEROSOL PROJECTOR (CO₂ system) has been designed for the effective diffusion of insecticidal fluids in a fine mist or cloud. The price of the projector is 52s. 6d., and the "C" sparklet bulbs 6s. per box of 12. (Sparklets Ltd., Upper Edmonton, London, N.18.)

THE WATERFIELD HALOMETER is designed for the measurement of red blood cells. A mercury arc in conjunction with an interchangeable green or yellow filter produces a monochromatic halo, and by using the method of Young a number of bright pinholes appear superimposed. The diameter of the cells can be read directly on the scale. (Kaylene Ltd., Waterloo Road, London, N.W.2.)

TUBERCULOSIS CONFERENCE

A COMMONWEALTH and Empire Health and Tuberculosis Conference will be held at the Central Hall, London, on July 5-8, 1949. Full particulars can be obtained from the Secretary, the National Association for the Prevention of Tuberculosis, Tavistock House North, Tavistock Square, London, W.C.1, from whom also copies of the Annual Report of the N.A.P.T., 1947-48, can be obtained.

PUBLISHERS' ANNOUNCEMENTS

The following pamphlets reprinted from material which originally appeared in **THE PRACTITIONER** are available exclusively to doctors for distribution to patients—

NOTES FOR THE PATIENT WITH INDIGESTION, 12 pp.

DIABETES FROM THE PATIENT'S POINT OF VIEW, 8 pp.

CONVALESCENCE AFTER HEAD INJURIES (advice for the patient's relations), 8 pp.

Price 6d. each, or 10 for 4s. 6d. and 50 for £1 1s. 6d. post free.

ADVICE IN CASES IN WHICH EXERTION CAUSES PAIN IN THE CHEST, 2 pp. Price 1d. each, postage extra.

BINDING CASES in green cloth with gilt lettering are available at 4s., post free. Each case holds one volume (six copies); they are not self-binding. Subscribers' copies can be bound at an inclusive charge of 10s. 6d. per volume; this includes the cost of binding case and return postage.

Erratum.—January issue, page 88, "Disparin" should read **DISPRIN**.

The contents of the March 1949 issue, which will contain a symposium on "Diseases of the Liver and Pancreas", will be found on page lxxiv at the end of the advertisement section.

THE PRACTITIONER

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THE MODERN CONCEPT OF CIRRHOSIS OF THE LIVER

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It is the purpose of this article to give a brief account of some of the advances that have been made in the study of hepatic disease during recent years, in so far as they bear upon the nature and causation of cirrhosis in man. Reference will also be made to the practical value of the aspiration needle biopsy technique in diagnosis. Treatment, biochemical aspects, and the problem of portal hypertension are dealt with elsewhere in this symposium. Readers desiring a more comprehensive exposition of modern views on cirrhosis and other forms of hepatic disease are advised to read the fully documented monograph by Himsworth (1947).

CLASSIFICATION

Since cirrhosis is the end-result of diseases the nature of which is not clearly understood, it is not surprising that classifications based on morphological grounds have been unsatisfactory. Bloomfield has likened the problem to that presented by chronic nephritis, which was formerly regarded as a pathological entity but is now known to be the sequel to a diversity of pathological conditions. As a broad classification the terms portal cirrhosis and biliary cirrhosis provide convenient designations because the majority of cases can be assigned to one or other of these groups, each of which tends to produce a distinctive clinical picture.

Portal cirrhosis, which is much the commoner type, produces clinical manifestations that are due to obstruction of the portal blood flow and to the consequent portal hypertension. This usually results in ascites, in splenomegaly, and in the development of varicose anastomotic channels between the systemic and portal venous systems. Hæmorrhage is a common feature, due to rupture of such varices in the gastro-æsoophageal region or in the rectum. The liver may or may not be enlarged. Often it is enlarged during the earlier phases of the disease and atrophies later. The skin is commonly pigmented, and a mild degree of icterus may be present; but frank jaundice is seldom seen.

The morphology of the liver in portal cirrhosis is variable. In the classical type originally described by Lænnec, and still associated with his name, the liver is shrunken and its surface is studded with coarse nodules. On section, the liver substance is seen to be intersected by strands of connective tissue. The resultant islets vary in size, and many of them comprise several hepatic lobules. To such a liver have been given the varied designations of Lænnec's cirrhosis, atrophic cirrhosis, multilobular cirrhosis, gin-drinker's liver, and hob-nail liver. The liver in portal cirrhosis may, however, differ significantly from that just described. Not uncommonly it is enlarged, the surface is finely granular, and the strands of fibrous tissue are narrower and more finely woven, so that the islets of liver cells are smaller and often monolobular. Fatty infiltration may also be a prominent feature. The occurrence of such large, fatty, and relatively finely cirrhotic livers is said to be associated with alcoholism. In other cases, the liver may be grossly deformed and show large irregular nodules circumscribed by broad bands of connective tissue. Many of the islets of liver tissue are composed of groups of apparently healthy lobules, whilst others are structureless masses of newly regenerated liver cells. In such livers the left lobe is commonly affected more extensively than the right. The distinctive features of this type of cirrhosis were first described by Mallory, who named it "toxic cirrhosis". The name "multiple nodular hyperplasia" has been given to a similar condition resulting from subacute yellow atrophy.

The majority of cases in this country show variations between the two extremes just described, but large livers are more common than textbooks would seem to indicate.

I am informed by Dr. Alexander Brown that in a series of cases of portal cirrhosis coming to autopsy at the Glasgow Royal Infirmary during recent years, of 42 consecutive cases in which œsophageal varices were demonstrated, 13 had enlarged livers weighing more than 1500 grammes.

It is therefore evident that portal obstruction is not necessarily related to the size of the liver. I must, however, admit that I do not know whether or not a multilobular pattern of fibrosis is invariably present in portal cirrhosis, irrespective of the size of the liver.

Biliary cirrhosis is characterized by a large liver and by a variable degree of jaundice of the obstructive type. Splenomegaly may occur; but ascites and other manifestations of portal hypertension are rarely seen. The liver is hypertrophied and presents a finely granular, bile-stained surface. On histological examination a periportal fibrosis is seen, which may extend and circumscribe the individual liver lobules. Proliferation of bile ducts is evident, and the bile canaliculi are distended with inspissated bile pigment. This type of cirrhosis is also called hypertrophic, or monolobular, cirrhosis. It will, however, be appreciated that portal cirrhosis may also be hypertrophic.

A number of other types of cirrhosis, or hepatic fibrosis, have been des-

cribed. Some of these present the general features of either portal or biliary cirrhosis, but are given distinctive appellations because of their relation to specific etiological factors, such as syphilis, helminthic infestations, hæmochromatosis, and glycogen disease. These will not be considered further here; nor will mention be made of Hanot's cirrhosis, except to state that it is highly doubtful if such an entity exists, and that most of the recorded examples of this condition were probably cases of biliary cirrhosis.

ETIOLOGY OF PORTAL CIRRHOSIS

The cause of portal cirrhosis has puzzled clinicians and pathologists since the days of Lænnec. The traditional importance of alcohol is symbolized by the term "gin-drinker's liver" commonly used for this condition. Despite the relative frequency of a history of chronic alcoholism in cases of portal cirrhosis, it has long been recognized that the condition may occur in teetotallers, and more recently it has been shown that it is common in various tropical peoples who do not drink alcohol. In experimental animals attempts to produce cirrhosis by the administration of alcohol have been unsuccessful, but the condition has often been produced by a number of organic and inorganic toxic agents. Although most of these poisons were unlikely to be concerned with its production in the human subject, it was thought that other unknown poisons or toxins, exogenous or endogenous, were usually responsible for its occurrence in man, and that alcohol might play an alternative, or predisposing rôle. It was believed that the toxic agent exerted its effect by killing the liver cells and by stimulating the proliferation of fibrous tissue.

Experimental evidence.—The above theory was widely accepted until some ten years ago, but since then, largely as the result of animal experimentation, ideas on the etiology of portal cirrhosis were modified, and it is now believed that the condition is commonly the result of changes initiated, or conditioned, by nutritional deficiency.

In laboratory animals it has now been shown that two distinct types of hepatic fibrosis can be produced by dietary deficiency:—(1) A fine diffuse fibrosis circumscribing the individual lobules throughout the liver, thus producing a monolobular cirrhosis. This type of lesion is preceded by fatty infiltration. (2) A coarse irregular fibrosis similar to multiple nodular hyperplasia. This is a sequel to massive necrosis and has therefore been termed "postnecrotic scarring".

Numerous investigators during the past ten years have shown that fatty changes in the liver can result from nutritional deficiency. Following the pioneer work of Best and his colleagues, it was found that the development of fatty livers in animals fed on high fat diets, or exposed to various hepatotoxic substances, could be prevented by certain dietary constituents, which were accordingly termed lipotropic substances. Conversely, diets deficient in these substances resulted in the rapid development of fatty infiltration. Choline was soon identified as an active lipotropic agent, and a few years later the sulphur-containing amino-acid, methionine, was found also to be active in this respect. Evidence has subsequently been presented which indicates that choline may be synthesized from methionine within the body. It has thus been established that fatty infiltration of the liver can be produced by

feeding certain animals on diets deficient in choline and methionine; and that when this dietary deficiency is prolonged, a diffuse hepatic fibrosis may result.

The precise nature of the mechanism whereby fatty infiltration leads to fibrous tissue formation is not clearly understood. It is possible that the accumulation of fat within the cell impairs its vitality and thus causes necrosis. Himsworth, while acknowledging this possibility, stresses the importance of the vascular factor. He points out that liver cells loaded with fat are swollen, and that this may cause a mechanical interference with the flow of blood in the intralobular sinusoids. It is suggested that the consequent slowing of the blood flow results in an undue proportion of nutrient substances being removed from the blood by the cells in the peripheral portion of the liver lobule, thus depriving the cells in the central portion of their share of essential nutrients, with the result that they eventually degenerate and disappear. If the injury be merely transient, regeneration of healthy liver cells occurs, but in continued injuries, as in long-standing fatty degeneration, regeneration is not possible and the lost cells become replaced by fibrous tissue.

Diffuse hepatic fibrosis of the same type as that resulting from fatty infiltration may also follow zonal necrosis of liver cells caused by a wide variety of hepatotoxic substances, but it usually occurs only after long-continued or repeated exposure, so that no opportunity is given for regeneration of liver cells to occur. Although, in this type of injury, it has been generally assumed that necrosis is caused by the direct action of the toxic agent upon the cells, it has always been difficult to explain why necrosis commonly begins in, or is confined to, the central portion of the lobule, instead of at the periphery where the cells are exposed to the highest concentration of the poison. Himsworth and Glynn believe that the explanation may lie in the vascular factor referred to in the preceding paragraph, for it has been shown that following an injection of a moderate dose of carbon tetrachloride, the earliest demonstrable effect is a swelling of the hepatic cells, and a marked impedance of the flow of blood in the sinusoids, with consequent ischæmia of the centrilobular cells. They accordingly suggest that the necrosis of these cells may actually be caused by deprivation of oxygen and essential nutriments such as cystine, and not by direct toxic action. This mechanism would also explain earlier observations by Whipple and others that the effects of certain hepatotoxic substances, such as chloroform, are aggravated by protein deficiency.

The second type of hepatic fibrosis, namely, postnecrotic scarring, was produced by Himsworth and Glynn in rats by feeding them for prolonged periods on diets deficient in protein and particularly in cystine which, like methionine, is also a sulphur-containing amino-acid. The rats, after remaining in apparent health for a lengthy latent period, developed massive necrosis of the liver, the appearances being similar to those seen in acute yellow atrophy in human beings. The lesions showed no zonal distribution, but consisted of large areas of dead tissue separated by areas of healthy tissue, and were not characterized by fatty change. The condition was commonly fatal, but in surviving animals the livers were found to be intersected, in

whole or part, by broad bands of fibrous tissue, resulting in large, irregular nodules, some of which were composed of structureless masses of newly regenerated liver cells, and others of groups of intact lobules. This multilobular appearance is considered by Himsworth to be a distinctive feature of postnecrotic scarring. It is believed that this type of liver injury may be specifically related to cystine deficiency.

It is noteworthy that the lesions were commonly more extensive in, or limited to, the left lobe of the liver. This is explained by the view that there are two distinct streams of blood in the portal vein, the right lobe receiving its blood supply from the small intestine, and the left lobe from the spleen and large intestine. The effects of nutritional deficiency will consequently be more marked in the left lobe.

NUTRITIONAL DEFECTS

The possible significance of the foregoing experimental findings in the causation of human cirrhosis may now be considered. That fatty infiltration may lead to cirrhosis in man has been established with reasonable certainty. Fatty changes have long been recognized as a common feature in portal cirrhosis, but it was not until 1938 that Connor produced evidence that the two conditions were causally related. Subsequent studies, notably by the Gillmans using the needle biopsy technique, showed that in African natives cirrhosis may gradually evolve from a preceding state of fatty infiltration attributable to severe and long-continued malnutrition. A number of other reports have confirmed that in various parts of the tropics and sub-tropics nutritional deficiency is not infrequently associated with fatty infiltration of the liver and fibrosis. It may therefore be accepted that portal cirrhosis of the diffuse type can occur in man as the result of nutritional deficiency.

The traditional association between *alcohol* and cirrhosis is now considered by many to be explicable on the basis of nutritional deficiency, because of the unsatisfactory dietetic habits so common in chronic alcoholics. Not only does alcohol contain no lipotropic factors, but its excessive consumption impairs the appetite and digestion, and its expense often results in an inadequate expenditure on the more valuable foodstuffs. Whether alcohol does also exert a direct deleterious effect upon the liver is unknown.

There is reason to believe that nutritional deficiency in man may also cause massive necrosis and its sequel, postnecrotic scarring. In its acute state it manifests itself by an illness resembling very severe infective hepatitis, showing the lesions of acute yellow atrophy, or massive necrosis, and is often fatal. This condition has been described in ill-nourished natives of tropical countries. Nodular hyperplasia, or postnecrotic scarring, has been observed subsequently in non-fatal cases, and is said to be relatively common in malnourished races subsisting on diets deficient in protein.

INFECTIVE AND TOXIC FACTORS

Massive hepatic necrosis has also been reported in acute infective hepatitis in patients whose diets were defective in protein. Although infective hepatitis is normally characterized by a zonal necrosis, it is probable that the occasional spread of necrosis to involve whole lobules may be due to

the combined effects of dietary deficiency and of the virus. In this connexion it should be mentioned that although there are good grounds for believing that cirrhosis may occasionally be attributed to an antecedent attack of infective hepatitis, it has not, so far as I am aware, been established that such cases are invariably of the postnecrotic type. The well-known relation of acute yellow atrophy to pregnancy is also possibly related to the nutritional inadequacy of many pregnant women.

Both the diffuse and the postnecrotic types of fibrosis have been reported in man following exposure to, or ingestion of, various toxic substances. It would seem that certain poisons such as carbon tetrachloride, chloroform, and arsenic may give rise to diffuse fibrosis if the exposure is prolonged or repeated, whilst others such as trinitrotoluene and cinchophen may result in massive necrosis and postnecrotic scarring. Since massive necrosis occurs in only a very small proportion of individuals exposed to such poisons, it has been suggested that the action of the poison may be conditioned by protein deficiency. Experimentally, there is ample evidence that dietary deficiency may render animals unduly susceptible to hepatotoxic substances.

OTHER PREDISPOSING FACTORS

Although there is satisfactory evidence that human portal cirrhosis may, in certain circumstances, result from nutritional deficiency, or from the action of certain toxic or infective agents, it must be admitted that in the majority of cases seen in this country the causative factor cannot be determined with certainty. Moreover, on morphological grounds, many cases of portal cirrhosis are difficult to assign to either of the classical types of fibrosis seen in experimental dietary deficiency. For it would appear that multilobular fibrosis, which Himsworth considers characteristic of postnecrotic scarring, is often present in livers which are uniformly cirrhotic and which are not typical of nodular hyperplasia. Furthermore, in such cases, there is often no history of previous acute illness suggestive of massive hepatic necrosis. Whether the presence of multilobular fibrosis necessarily has the same significance in man as it has in rats remains to be ascertained. Nevertheless, it must be borne in mind that mixed lesions have been produced experimentally by diets deficient both in lipotropic factors and in cystine, and that these may well occur in man. It would seem not improbable that once a cirrhotic process has begun, irrespective of its initial cause, its subsequent course may be susceptible to modification or acceleration by various secondary influences. Thus, it has been shown that fibrosis is apt to cause a gross distortion of the hepatic vascular channels, so that a considerable proportion of portal blood is short-circuited and does not reach the liver cells. This mechanical interference with the oxygenation and nutrition of the cells is alone sufficient to create a vicious circle, and so explain the progressive nature of cirrhosis; but, as already suggested, it would also tend to accentuate the baneful effects of incidental nutritional or toxic factors,

although these might be insufficient to cause permanent lesions in a healthy liver. An established fibrosis of one type might thus be complicated by a secondary fibrosis of another type. The analogy with chronic nephritis would seem to be particularly pertinent here.

Summarizing the present position, it would appear that there are substantial reasons for believing that nutritional deficiencies may play a significant part, either in causing, or in adversely influencing, portal cirrhosis in man. Deficiency in lipotropic factors tends to produce a diffuse type of fibrosis, whilst severe protein deficiency may give rise to the coarse multilobular type. Acting concurrently or consecutively they may produce a mixed type of lesion. It is likely that cirrhosis may also result from the combined action of a nutritional and of a toxic or infective factor, either of which might be ineffective acting independently. It remains to be determined, however, to what extent the various factors known to be capable of producing cirrhosis are in fact involved in the majority of cases seen in this country. It would, at present, seldom appear justifiable to incriminate any specific cause on the basis of post-mortem findings.

A point that does not seem to have received due consideration, either in animal experiments or in clinical studies, is the extent to which the development of cirrhosis may be influenced by *genetic factors*. It is perhaps significant that Himsworth and Glynn found that different strains of laboratory rats varied significantly in their susceptibility to nutritional deficiency. In human medicine the examples of many other diseases provide support for the possibility that different individuals may vary innately in their susceptibility to liver injury.

BILIARY CIRRHOSIS

Biliary cirrhosis is usually attributable to a chronic low-grade bacterial infection ascending the bile ducts secondary to a long-standing partial obstruction to the biliary outflow. The obstruction commonly affects the large bile ducts outside the liver, and may be due to causes such as biliary calculi, tumours, or inflammation. The effect upon the liver is to cause a cellular infiltration which spreads out from the portal tracts and later becomes replaced by fibrous tissue. The fibrous tissue may eventually extend from the portal tracts so as to circumscribe the liver lobules, thus giving rise to a so-called monolobular cirrhosis. Proliferation of the bile ducts also occurs. The bile canaliculi tend to be distended with inspissated bile pigment, and the hepatic cells become bile-stained. These processes result in a generalized enlargement of the liver, which presents a finely granular, bile-stained appearance.

Since the pathological processes which may give rise to biliary cirrhosis vary greatly in severity and in speed of development, the immediate effect is also very variable. On the one hand, the condition may progress rapidly to a fatal suppurative cholangitis, whereas on the other hand it may per-

sist for years before the development of clinically recognizable cirrhosis. Despite this variability, since the underlying pathological process is in all cases fundamentally similar, Himsworth advocates the use of the term "cholangio-hepatitis" for its description. According to this designation, biliary cirrhosis should be regarded as synonymous with chronic cholangio-hepatitis. Although cholangio-hepatitis can occur in the absence of demonstrable obstruction to the larger bile ducts, some degree of biliary obstruction is probably always present.

From the practical point of view it is necessary that the importance of the obstructive factor should be borne in mind, and that in all cases in which it is suspected, a laparotomy should be performed, unless it is reasonably certain that the cause of the obstruction is inoperable.

ASPIRATION NEEDLE BIOPSY IN THE DIAGNOSIS OF CIRRHOSIS

Space does not allow a description of the technique of this procedure. For this, the articles by Sherlock (1945) and Harris (1948) may be consulted. It has already proved most valuable as a research tool in studying the pathogenesis of cirrhosis as well as that of other diseases of the liver, and is often of value in clinical diagnosis. Only its application in this latter connexion will be considered here.

With the modern small-calibre cannula, the procedure is reasonably safe if all appropriate precautions are observed. It has been performed under my direction on over a hundred occasions during the past three years without mishap. Nevertheless, it should obviously be employed only in cases in which it is considered that the information it is hoped to obtain justifies the slight risk involved. Unfortunately, the results are not always conclusive. In the first place, puncture of a hard cirrhotic liver may fail to yield an adequate specimen of tissue. Although this eventuality can be minimized by ensuring that the edge of the cannula is sharp, it seems that occasionally even a sharp needle may not succeed in removing a satisfactory core of tissue if the fibrosis is abundant and dense. In the second place, since the specimen is small, it may fail to reveal fibrosis or other pathological lesion if it is distributed irregularly. In the majority of cases of cirrhosis, however, needle biopsy will provide definite histological evidence of its presence, and may give valuable information concerning its type.

As indications of the clinical problems that may be solved by liver biopsy, the following examples may be cited:—

(1) *Hæmatemesis* in a patient with no evidence of peptic ulcer or of other obvious cause may be shown by liver biopsy to be due to cirrhosis. Obviously such a case should first be investigated radiologically for evidence of oesophageal varices, but when these are present they are not always demonstrable by X-rays. Moreover, when they are demonstrated, thus establishing

the existence of portal hypertension, it does not necessarily follow that this is due to cirrhosis, even if splenomegaly also be present. It may be due to thrombosis or other obstruction in the portal or splenic vein. Therefore in such a case, unless clinical examination of the liver reveals cirrhosis, needle biopsy may be well worth while, especially if one of the new operative procedures for the relief of the portal hypertension is contemplated.

(2) In a patient with a large firm liver, it may occasionally be uncertain on clinical grounds whether the cause is cirrhosis or cancer. Needle biopsy may settle the question by demonstrating cancer tissue. In other cases the information obtained may be inconclusive, but it may still be helpful. The cancerous areas may be missed by the needle and a specimen of normal liver tissue be obtained; this, in such a patient, would favour a diagnosis of carcinoma rather than of cirrhosis. On the other hand, if cirrhotic tissue is obtained, although this does not exclude the presence of carcinoma, it renders it less likely. Primary carcinoma of the liver is often associated with cirrhosis, but its rarity in this country seldom justifies its diagnosis in the absence of positive evidence. Nevertheless, I have had two patients during the past two years in whom primary hepatic carcinoma was revealed by needle biopsy. Needle biopsy may reveal other causes of hepatic enlargement, such as Gaucher's disease and amyloid disease. It also provides a convenient means of establishing the diagnosis of hæmochromatosis.

(3) After a severe attack of hepatitis, due either to infection or poison, there may be some doubt whether recovery is complete. Liver biopsy may resolve the doubt by showing either healthy liver tissue or early fibrotic changes. This information may clearly be of value, not only in prognosis but in enabling the physician to prescribe an appropriate regimen.

(4) Finally, needle biopsy may provide information of great practical value in the diagnosis of early biliary cirrhosis. It may be extremely difficult on clinical grounds to distinguish this condition from parenchymatous hepatitis, but the histological appearances of the two conditions are distinctive. The recognition of cholangio-hepatitis or biliary cirrhosis as early as possible is highly desirable, because if the obstructive factor is removable, the further progress of the disease may be, and indeed should be, prevented by timely surgical intervention.

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THE TREATMENT OF HEPATITIS AND CIRRHOSIS

By R. E. TUNBRIDGE, O.B.E., M.D., M.Sc., F.R.C.P.

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THE essential defect in both hepatitis and cirrhosis is liver damage. The aim therefore of all treatment is to assist in the restoration of normal liver function.

HEPATITIS

The most common form of hepatitis is infective hepatitis, often referred to in the past as catarrhal jaundice. It is essentially an infective disease of children characterized by an abrupt onset with headache, fever, malaise, gastro-intestinal symptoms, notably anorexia and vomiting, and followed later by jaundice. During the recent world war, epidemics occurred among the troops of all nations, and to-day many think of the condition as one affecting adults rather than children. No age-group is in fact immune. A number of the outbreaks among Service personnel were due to homologous serum jaundice, a similar virus disease to infective hepatitis, but characterized by a longer incubation period, sixty to one hundred and twenty days, and a more insidious onset. Finally, there is the important group of cases of toxic hepatitis due to chemical substances, such as arsenic, phosphorus, cinchophen, bismuth, chloroform, trinitrotoluene, and gold. The clinical course in the milder cases of the latter group may be indistinguishable from that of infective hepatitis or homologous serum jaundice, but there is a greater tendency for the subsequent development of subacute yellow atrophy or acute liver necrosis.

Treatment

No specific therapy is available for the treatment of hepatitis. In a case of toxic hepatitis the first essential is to remove the patient from all risk of further exposure to the noxious agent. This done, the treatment of all forms of hepatitis can be summarized under the headings: rest in bed, diet, and symptomatic measures.

Rest in bed.—The duration of rest in bed will depend upon the severity of the illness. In mild cases, jaundice of less than three weeks' duration, it is advisable to keep the patient completely at rest in bed until a sample of early morning urine has yielded a negative Fouchet test on three consecutive mornings. In the more severe cases it is recommended to wait until the Fouchet test has been negative on seven consecutive mornings before allowing the patient to get up.

The technique of the Fouchet test is as follows:—

Fouchet test.—Reagents: 10 per cent. barium chloride, Fouchet's reagent (25 g.

trichloroacetic acid, distilled water 100 ml., and 10 ml. of 10 per cent. ferric chloride). Test: take 10 ml. (2" in an ordinary test tube) of urine sample, acidify with acetic acid and add approximately 5 ml. of 10 per cent. barium chloride solution. Mix and filter. After filtration, open up the filter paper on a tile, or another dry filter paper, and drop on to it a drop of the Fouchet reagent. A green or blue colour denotes the presence of bilirubin. For further details see Harrison's "Chemical Methods in Clinical Medicine" (1947), 3rd edition, London.

The duration of further convalescence will of course depend upon the severity of the illness, the rate of recovery, and the nature of the patient's work. No hard and fast rules can be laid down; each case must be judged separately. Many children have such a mild attack that it is difficult to persuade the relatives to keep the child in bed even at the onset.

Liver biopsy studies made by Mallory (1947) on twenty normal convalescents, at periods ranging from thirty-four to one hundred and thirty-one days after the onset of disease, yielded seven with normal histological findings, five with minimal pathological changes, and eight with evidence of periportal and intralobular inflammatory infiltration.

It would therefore seem fair to conclude that clinical recovery is not necessarily accompanied by the complete restoration of liver function to normal. In consequence, considerable discretion should be exercised in determining the duration of convalescence. Generalizing: a patient with a history of three weeks' jaundice and employed in heavy industry or on Active Service is unlikely to be fit for full duty for at least two to three months after the disappearance of the jaundice. On the other hand, a patient engaged in clerical, scholastic, or light manual duties, might be fit to return to work within one month of the disappearance of jaundice.

Diet.—The essential modern dietary treatment of hepatitis is the provision of a diet adequate in calories and protein. During the pre-icteric phase, and in some instances for long periods during the icteric phase, there is a pronounced aversion to food. Careful nursing and coaxing, together with the expenditure of much time, thought and patience upon the mode of presentation of the food, afford the only way of getting such a patient to maintain an adequate calorie intake. In the past it has been traditional to prescribe a low fat diet; a truly low fat diet is most insipid and, since recent work has shown that moderate amounts of animal fat are not harmful to the damaged liver, there is no need to prescribe a low fat diet unless the patient refuses to take the normal ration of milk, butter, and lean meat. The calorie value of the diet should be approximately 3000 to 3500 calories, made up of 100 to 120 g. protein, 300 to 400 g. carbohydrate, and 100 to 120 g. fat—in other words, the type of diet taken by a reasonably well-to-do middle class family pre-1939. The attainment of such a standard is difficult to-day, but the position has been helped by the granting of two extra rations of meat for patients suffering from hepatitis. The extra ration is obtainable on a doctor's certificate for four weeks in the first instance and is renewable thereafter up to sixteen weeks, if necessary. To attain a protein intake of 120 g. a day a patient requires to have meat or fish at three meals, or at two meals with the addition if possible of a pint of milk a day.

Glucose and glucosade are frequently prescribed and often demanded. It should be stressed that glucose apart from its greater assimilability has no particular virtue over other forms of carbohydrate and if taken too freely may cause nausea, with serious detriment to the patient's total calorie intake. Experimental studies have shown that methionine and choline exert a beneficial effect upon the restoration of liver function. The work of Wilson and co-workers (1945) did not suggest that methionine had any beneficial effect upon the recovery rate in cases of infective hepatitis, although Peters and co-workers (1945) did obtain statistically significant improvement in the treatment of post-arsphenamine jaundice following the administration of cystine and methionine but not with casein. The absence of any dramatic response to the administration of methionine, cystine, and casein digest suggests that such adjuvant therapy is not essential for the treatment of the ordinary case of hepatitis.

Alcohol.—A special reference must be made to alcohol. There is a considerable difference of opinion as to the possible injurious effect of alcohol. Damodaran and Hartfall (1944) were definitely of the opinion that alcoholic indulgence during convalescence led to an increased tendency to relapse. It would seem advisable to recommend all patients to refrain from alcohol for at least three, and preferably for six, months after an attack of hepatitis.

Symptomatic treatment may be required for intense pruritus, headache, sleeplessness, indigestion, and colic. There is no specific therapy for the itching. It is usual to prescribe calamine lotion with 2 per cent. of phenol, for local application, and to give calcium gluconate either orally or 5 to 10 ml. intramuscularly each day. In the treatment of the headache and sleeplessness, aspirin, 10 grains (0.65 g.), compound tablets of codeine, or phenobarbitone, $\frac{1}{2}$ a grain (32 mg.) t.d.s., are usually effective. Drugs with a possible toxic effect upon the liver, or mainly metabolized in the liver, such as morphine, should be avoided. Post-icteric indigestion, comprising upper abdominal discomfort, often postprandial and associated in some instances with pain in the left hypochondrium and subcostal region, may prove exceedingly troublesome. The symptoms usually settle within three months, but the prescribing of a modified peptic ulcer diet, together with the judicious use of sedatives, often assists in their alleviation. There is no need to submit the patient to an elaborate gastro-intestinal investigation unless there are specific indications for so doing. Attacks of colic occurring during convalescence and presumably renal in origin are rare but very disconcerting to the patient. They are assumed to be due to intrarenal hæmorrhage and are adequately dealt with by placebo measures and reassurance, unless other clinical indications of renal damage occur, when a complete renal investigation is necessary.

PREVENTION AND PROPHYLAXIS

The greatest care should be taken in the sterilization of syringes. All syringes and needles used for injections or likely to be contaminated with serum

should be used for one patient only and then thoroughly sterilized, preferably by autoclaving.

Experience has shown that the administration of *human gamma globulin* up to six days before the onset of symptoms will afford protection against infective hepatitis for a period of at least six to eight weeks (Havens, 1948). The preparation used is normal human gamma globulin in a dosage of 0.06 to 0.12 ml. per pound (0.45 kg.) of body weight, or roughly 10 ml. for an adult of average weight. It would hardly seem practical to do this as a routine, but its use should be considered when patients over the age of forty suffering from some debilitating disease have been exposed to contact with an infected person, or in V.I.P.'s. or combat troops about to embark upon a special mission.

CIRRHOSIS

Cirrhosis is usually taken to refer to multilobular, Lænnec's or gin drinkers' cirrhosis, a condition more frequently met with in hospital than in general practice. The condition is often found among teetotallers and cannot any longer be considered as being due to an alcoholic excess. Recent reviews by Himsworth (1947) and in this issue by Davis (1949) have stressed the diversity of conditions which have hitherto been classified as cirrhosis, and also the importance of nutritional factors, particularly a deficiency of protein intake, in predisposing to liver damage, both in the experimental animal and in man. For the purpose of treatment, in the present article, cirrhosis will be defined as chronic hepatitis complicated by mechanical factors.

Diet.—Patek and co-workers (1948) have made an extensive study of the effect of diet upon the clinical course of cirrhosis in man and in experimental animals, and have analysed their results over the past ten years:—

Of 124 patients treated, 61 showed definite clinical improvement as evidenced by (1) the disappearance of ascites, jaundice, and œdema; (2) the gain in weight and strength; and (3) the improvement in tests of hepatic function. The dietary basis of the regime was the giving of an adequate diet with a calorie value of approximately 3500, comprised of 140 g. of protein, 365 g. of carbohydrate, and 175 g. of fat, the diet consisting chiefly of milk, meat, eggs, fruit, and green vegetables. Eggs were served with breakfast; meat, fish or poultry at dinner and supper; milk at three meals a day and twice between meals. By way of supplement the patients were given orally a vitamin B complex or, if they could tolerate it, dried yeast, 25 g. per day. In addition they were given 5 mg. daily of thiamine hydrochloride and 5 ml. of an unconcentrated liver extract twice weekly, both intramuscularly. In cases with profound anorexia and mental symptoms, the doses of thiamine were increased to 100 mg., and in addition nicotinamide, 300 mg., was injected daily.

Such a diet is obviously not possible in this country unless one has access to plentiful supplies of fish and vegetables or to farm produce. Two additional meat rations per week are permitted on a doctor's certificate for twelve weeks in the first instance and are renewable. In many patients anorexia and mental irritability are so marked that the primary consideration is to induce the patient to eat. The remarks made above on this point in relation to hepatitis apply equally to cirrhosis of the liver. Casein digest, choline, 4 to 6 g. daily, and methionine, 3 to 4 g. daily, have been given but

there is no report with adequate controls to justify their prescription as a routine procedure. The regular administration of liver extract is a valuable adjuvant to therapy and any reliable preparation may be used, although some workers prefer the less highly refined extracts; a daily intramuscular injection of 2 to 4 ml. is recommended. Diets deficient in the vitamin B complex have led to the production of cirrhosis in experimental animals and, although there is as yet no reliable confirmation of this work in man, there would seem to be no contraindication to the giving of vitamin B concentrates in the treatment of cirrhosis. Many workers prefer the administration of crude extracts or yeast rather than refined products, but it is often difficult to induce patients to take doses of yeast of the order of 25 g. daily, owing to the nauseating taste. In such instances the use of purified preparations would appear to be justified. Patients with a low blood protein concentration, whether or not ascites and œdema are present, may benefit from the intravenous administration of concentrated plasma or, if available, of concentrated serum albumin (Patek, 1948).

During the acute exacerbations of illness patients will naturally desire to remain in bed, but during convalescence they should be encouraged to get up as much as their general condition permits. Alcohol should be barred, but in the case of chronic alcoholics it is advisable to reduce the intake gradually in order to prevent the development of delirium tremens.

Hæmatemesis due to hæmorrhage from a ruptured œsophageal varix may occur at any stage of the disease and the treatment will depend upon the severity of the hæmorrhage. In severe cases a constant drip blood transfusion of suitably matched blood should be instituted without delay. The ordering initially of morphine, $\frac{1}{4}$ of a grain (16 mg.), is justifiable to allay the patient's fear, but the dose should not be often repeated as morphine is not well tolerated by cirrhotic patients. Furthermore, the effects of the morphine may mask the development of cholæmia, the latter being not infrequently precipitated by a severe hæmorrhage. During the first few days the food intake should be confined to fluids by mouth, but after three days, if the patient's condition permits and no other cause for the hæmatemesis be present, the diet can rapidly be restored to normal.

Ascites is another important complication of cirrhosis calling for special treatment. In the first instance the effect of a restricted fluid intake, not more than three pints daily, with the restriction also of salt intake, such as avoidance of salt in cooking and as a condiment with food, may prove effective. Should these measures fail, mercurial diuretics, such as mersalyl 0.5 ml., may be tried with or without the previous administration of ammonium chloride in a dosage of 4 to 6 g. Should no diuresis be obtained following a second dose of 2 ml. of mersalyl, mercurial therapy should be stopped, and recourse must be had to paracentesis. The details of paracentesis abdominalis are fully described by Learmonth (1946). Recurrent ascites has led to the introduction of more radical surgical treatments with a view to establishing a collateral circulation. The Talma-Morison operation

has now been discarded, but anastomoses between the left renal and splenic veins and between the portal vein and the inferior vena cava are in vogue, and their place in therapy is discussed in this issue by Milnes Walker (1949).

Intercurrent infection used to account for 25 per cent. of all deaths in cirrhosis of the liver but the discovery of the sulphonamides and the antibiotics has reduced the mortality considerably. Penicillin is preferable to the sulphonamides, as liver damage has been reported following the use of sulphonamides (Watson, 1940).

CHOLÆMIA

Cholæmia is the most serious of all the complications of cirrhosis and is often the immediate cause of death. It occurs rarely in infective hepatitis and homologous serum jaundice but is more frequent in toxic hepatitis. Cholæmia calls for intensive emergency therapy. Fluids should be administered intravenously in the form of 10 per cent. glucose in half normal saline. At least 3 litres should be administered in the first twenty-four hours. If more fluid is given, glucose only should be used in order to avoid salt retention. Oxygen, administered by means of a B.L.B. mask, may prove beneficial. Hæmorrhage is liable to occur, due to hypoprothrombinæmia. To counteract this a blood transfusion may be given or vitamin K, administered in 5 mg. doses intramuscularly twice daily. Methionine, 5 to 10 g. may be added to the intravenous infusion, as may vitamin B concentrates; thiamine hydrochloride, 100 mg. per litre, nicotinamide, 300 mg. per litre, riboflavin, 100 mg. per litre, and liver extracts, 5 ml. of a reliable intravenous preparation once daily. Blood loss, due to hæmatemesis, is corrected by a continuous drip transfusion. Intercurrent infections are treated by penicillin in large doses. The treatment described is continued until the patient is able to take food orally.

CONCLUSION

It must be reiterated that both hepatitis and cirrhosis are merely clinical syndromes brought about by many etiological agents. The immediate treatment can only be aimed at correcting the presenting derangements of liver function. Long-term therapy and prevention will not be possible until more is known concerning the etiological factors.

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SURGERY OF THE PANCREAS

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THE diseased pancreas, by virtue of its intimate visceral and vascular relationships and its manifold physiological functions, is capable of versatile clinical expression and is productive of profound metabolic derangement. In this resumé of surgery of the pancreas, some of the clinical problems presented are admittedly rare and may not be encountered except in clinics dealing with a considerable volume of pancreatic disease, but their inclusion here is justifiable in terms of completeness and in the stimulation of increased interest in pancreatic disorders. This clinical discussion of surgical diseases of the pancreas is based chiefly on observation and treatment of patients seen at the Lahey Clinic and does not include a review of the literature.

CLASSIFICATION

Pancreatic diseases of surgical interest may be classified as follows:—

(1) *Congenital abnormalities*

- (a) Ectopic pancreas
- (b) Annular pancreas
- (c) Congenital cysts
- (d) Fibrocystic disease of the pancreas

(2) *Inflammation*

- (a) Acute
 - (i) Acute pancreatic œdema
 - (ii) Acute pancreatic necrosis
- (b) Chronic
 - (i) Chronic relapsing pancreatitis
 - (ii) Pancreatic lithiasis and pancreatic calcinosis
 - (iii) Cysts of inflammatory origin
 - (iv) Inflammatory fistula

(3) *Traumatic*

- (a) Hæmorrhagic cysts
- (b) Fistula

(4) *Tumours*

- (a) Adenomas
 - (i) Benign
 - (ii) Malignant
- (b) Benign tumours
 - (i) Cyst
 - (ii) Cystadenoma
- (c) Carcinoma of the pancreas and ampulla of Vater

CONGENITAL ABNORMALITIES

Ectopic pancreas.—Isolated masses of pancreatic tissue have been found in many abdominal organs. As would be anticipated, they are more common in the stomach, duodenum and upper jejunum, although instances of aberrant pancreas involving the ileum, biliary tract, mesenteries and spleen have been reported. Ectopic pancreatic rests vary in size, but show normal histological architecture. They are, for the most part, non-symptomatic and are often found only at autopsy. Occasionally they may occur near the pylorus and attain sufficient size to produce obstructive symptoms or appear as suspicious filling defects in the barium contrast skiagrams of the stomach and duodenum. Instances of small bowel obstruction caused by ectopic pancreatic masses have been reported. It is important to be mindful of these lesions in assessing obscure tumours of the gastro-intestinal tract.

Annular pancreas is a rare anatomic anomaly. The cumulative literature records approximately 50 instances of this abnormality, and in 39 of these cases the finding was incidental to post-mortem examination. Eleven patients had sufficient symptoms, presumably related to the deformity, to warrant clinical investigation. A correct preoperative diagnosis has been made on one occasion in the case reported by Lehman (1942). The lesion may be missed entirely during abdominal exploration, or its true nature revealed only after painstaking dissection. The deformity results from improper rotation of the ventral limb of the embryonal pancreas with fusion of the two limbs about the second portion of the duodenum. The duodenum may be partially or completely obstructed.

When *symptoms* occur referable to the lesion they are usually related to (1) chronic pancreatitis, (2) peptic ulceration, or (3) obstruction of the duodenum. Radiological studies following a barium meal may reveal partial obstruction of the second portion of the duodenum, with notching of the lateral aspect. Varying degrees of gastric retention occur.

The treatment of symptomatic annular pancreas is surgical, and may consist in either (1) division or resection of the annular portion of the gland, (2) a gastro-enterostomy, or (3) a duodeno-jejunostomy. The presence of active peptic ulceration may indicate a subtotal gastrectomy. Division or partial resection of the deformed portion of the gland is dangerous in that this procedure may result in a pancreatic fistula or it may interrupt the continuity of the main pancreatic duct with the duodenum. Duodeno-jejunostomy appears to be more feasible than gastro-enterostomy in the presence of duodenal obstruction without peptic ulceration.

Case 1.—A male, thirty-seven years of age, was first seen in the clinic in 1932, at which time he complained of chronic, recurrent, periodic pain in the epigastrium of fourteen years' duration. Studies at that time showed a deformity of the proximal duodenum with moderate gastric retention and severe hyperchlorhydria. He responded to an adequate ulcer management. He returned to the clinic in November 1946 with the same complaints, and related that he had had frequent bouts of recurrent ulcer distress during the intervening years. Recently the pain had become more constant and nausea and vomiting had appeared. X-rays of the stomach and

duodenum following a barium meal showed a constant constricting deformity of the cap and narrowing of the second portion of the duodenum. A diagnosis of penetrating duodenal ulcer was made and operation advised.

At operation, in February 1947, the duodenal cap was scarred and contracted. Beyond this point the duodenum was encircled by an annular segment of pancreas. The anterior portion of the annular segment of pancreas was excised and a subtotal gastrectomy, cholecystectomy and choledochostomy performed.

The postoperative course was extremely prolonged and hectic. A pancreatic fistula ensued; the wound disrupted and a jejunal fistula occurred following the secondary closure of the wound. The pancreatic fistula healed spontaneously but the jejunal fistula required subsequent operative closure. Ultimate recovery with satisfactory clinical results followed the final operation.

Comment: The wisdom of dividing the annular portion of the pancreas must be questioned in this instance. A gastro-enterostomy combined with bilateral sub-diaphragmatic vagotomy would have been less hazardous and might have offered adequate relief of symptoms.

Congenital cysts of the pancreas are extremely rare. Dermoid cysts have been reported, as have multiple cysts of the pancreas associated with congenital cystic disease of the kidneys or liver. It is feasible to excise dermoid cysts, but multiple congenital cysts of the pancreas have not, to our knowledge, been resected.

Fibrocystic disease of the pancreas is congenital. Often it is familial, and instances involving twins have been reported. It is characterized pathologically by obstruction of the pancreatic ducts and multiple cyst formation. The islands of Langerhans are usually normal. There may be associated congenital lesions of the gastro-intestinal tract. The symptoms include failure to gain weight, steatorrhœa, and repeated attacks of respiratory infection. The celiac syndrome persists in those patients who survive. The treatment includes a high protein diet and the restriction of carbohydrates and fats. Supplements of fat-soluble vitamins and pancreatic extracts should be administered.

INFLAMMATORY CONDITIONS

Acute inflammatory reactions of the pancreas, commonly designated acute pancreatitis, may occur pathologically in the form of acute pancreatic œdema, which is relatively mild in its clinical manifestations, or as acute pancreatic necrosis associated with devastating clinical symptoms. The latter form of the disease may progress to suppuration and abscess formation.

The *etiology* of acute pancreatitis remains speculative despite the general acceptance of the theory of the causal relationship of the reflux of bile into the pancreatic ducts secondary to obstruction of the common duct, resulting from an impacted stone or from spasm of the sphincter of Oddi. More plausible, perhaps, is the possibility that the infection may reach the pancreas by direct extension from the duodenum by way of the pancreatic ducts or by lymphatic or hæmatogenous spread. Probably some degree of obstruction of the pancreatic ducts is necessary for its development. Alcoholic excess is a common historical precedent to the disease, and biliary lithiasis plays a provocative accompaniment in a majority of cases.

The *signs and symptoms* of acute pancreatitis are extremely variable and often lack diagnostic precision. It is possible, however, to recognize the disease clinically in most instances wherein pancreatic necrosis exists, by a careful appraisal of the sequence of the symptoms and signs. The sudden onset of severe, persistent epigastric pain initiates the attack. The pain is aggravated by the ingestion of food or water and is particularly refractory to average doses of narcotics; it is followed by repeated waves of nausea and vomiting and later by obstipation and progressive abdominal distension.

The physical signs include localized epigastric tenderness and rigidity, which become generalized and extreme as the disease progresses. Peristalsis gradually diminishes and ultimately disappears, followed by an insidious and persistent abdominal distension. Palpable tenderness in the region of the pancreas will appear within a few days of the onset of the illness, if severe pancreatic necrosis occurs. Fever is moderate and remittent. Clinical shock, cyanosis and collapse, features which were given great prominence in the early literature pertaining to acute pancreatitis, are, on the contrary, relatively rare. Demonstrable degrees of hæmo-concentration and diminished blood volume are common and diagnostically helpful. Jaundice occurs in the severe forms of the disease and probably reflects an associated hepatitis rather than an obstruction of the common duct. Cullen's and Grey-Turner's signs, an ecchymotic discoloration of the skin of the peri-umbilical and flank areas respectively, and indicative of retroperitoneal hæmorrhage, occur in approximately 10 per cent. of cases and are a late confirmatory sign of the disease.

Laboratory findings include nonspecific leucocytosis with increase in the granulocytes, and elevation of the hæmoglobin and hæmatocrit values early in the disease. The demonstration of a significant elevation of the amylase content of the blood and urine is diagnostic of acute pancreatitis. The increased amylase activity in the serum occurs rapidly, reaches a maximum concentration within forty-eight hours, and then declines rapidly to normal. The elevated finding in the urine persists for a longer period and is a more helpful diagnostic aid when the patient is first seen late in the disease. Hyperglycæmia, glycosuria, and diabetic glucose tolerance curves occur in the devastating forms of the disease and should be searched for in all instances of acute pancreatitis. Hypocalcæmia has been observed.

The *treatment* of acute pancreatitis is non-operative if the clinical diagnosis can be established with reasonable certainty. When the diagnosis is in doubt, early laparotomy is preferable. This is the only means of excluding perforation of peptic ulcer or gall-bladder in certain cases. Deliberate surgical intervention in the presence of recognized acute pancreatitis is reserved for those instances in which the inflammatory process goes on to suppuration or cyst formation. If operation is performed during the acute phase of the disease the procedure should be limited to the insertion of a drain into the lesser peritoneal sac and the introduction of a T-tube into the common duct if the extrahepatic biliary tree is distended.

The conservative management of acute pancreatitis comprises the relief of pain by (1) the administration of adequate doses of narcotics and antispasmodics, and paravertebral injection of procaine in the region of the splanchnic nerves; (2) the restoration of normal blood volume by the utilization of plasma, whole blood and glucose-saline solutions; (3) the prevention of distension by early intubation and continuous suction of the small bowel; and (4) the detection and appropriate treatment of diabetes mellitus, suppuration and cystic accumulations.

Case 2.—A male, seventy-three years of age, was admitted to the hospital on August 2, 1947, twenty-four hours after the onset of severe epigastric pain and persistent vomiting. The patient was acutely ill, despite normal temperature, pulse and respiration. The abdomen was flat and moderately tender throughout. Peristaltic activity was normal and no masses were palpable. An X-ray of the abdomen was negative. The hæmoglobin was 16.8 g. per 100 ml. The urine contained 1 plus albumin and 3 plus sugar. The fasting blood sugar value on the following morning was 210 mg. per 100 ml., the serum amylase was 600 units and the serum bilirubin was 3.4 mg. per 100 ml.

A diagnosis of acute pancreatitis was made and conservative measures, consisting of the liberal administration of morphine, adequate amounts of plasma, whole blood and glucose-saline solutions, and sufficient doses of insulin to control the diabetic state, were instituted. Distension was controlled by Miller-Abbott intubation.

The patient pursued an extremely toxic course for three weeks. Grey-Turner's sign appeared on the sixth hospital day and a tender, irregular mass became evident in the epigastrium at the same time. The toxicity gradually subsided, intestinal activity was resumed, and the diabetic state stabilized. The patient was discharged from the hospital on September 24, 1947, free from pain and gaining weight. The diabetes is controlled with 20 units of protamine zinc insulin daily.

Comment: This case demonstrates many of the classical features of severe pancreatic necrosis. The extreme pain, the sustained vomiting, and the maintenance of normal blood pressure values are typical findings. The diminished blood volume, the high serum amylase concentrations, and the interference with glucose metabolism reflect the seriousness of the disease. The persistent ileus, the ecchymosis in the flank, and the upper abdominal mass substantiate the diagnosis. The necessity of anticipating the sequence of the clinical manifestations of the disease in order to plan a rational, non-operative management is obvious.

Chronic relapsing pancreatitis was first presented as a clinical entity by Comfort and his associates in 1946. The term was used to describe a symptom complex characterized by recurrent bouts of upper abdominal pain, associated with, or followed by, demonstrable disturbances in function of both acinar and islet tissue. The disease often progresses to a chronic state complicated by fibrosis and calcification, leading to persistent pain, steatorrhœa and diabetes. Pathologically, the disease appears to be the result of recurrent attacks of varying degrees of acute pancreatitis, wherein the pancreas may show areas of œdema, hæmorrhagic necrosis, cystic degeneration, fibrosis, atrophy, and calcification. The disease may precede or follow the development of cholelithiasis.

During the acute phases of the disease the *symptoms* are identical with those of acute pancreatitis. Later the pain becomes more persistent and the

reference of the pain more diffuse. Anorexia, nausea and vomiting, and diarrhoea occur and account for the progressive deterioration in the nutritional status of the patient. The victims often resort to excess use of alcohol and narcotics. The physical findings vary considerably as the symptoms reflect the change from the quiescent to the relapsing phase of the disease. Between attacks there may be no positive physical signs. When the symptoms flare up there will be tenderness and spasm in the epigastrium, low-grade fever, perhaps jaundice, or a palpable cystic or indurated mass in the region of the pancreas.

Significant laboratory data include the demonstration of undigested fat and unaltered meat fibres in the stool, and the elevation of the serum and urinary diastase during the clinical relapse. Many victims will show hyperglycæmia, glycosuria, and glucose tolerance curves typical of diabetes mellitus.

Radiological studies will reveal the presence of pancreatic calculi or diffuse calcification in approximately 50 per cent. of cases. Skiagrams following a barium meal may reveal widening of the duodenal sweep or evidence of extrinsic pressure on the stomach, if pancreatic cysts are present. Not infrequently the diagnosis is established only by surgical exploration, at which time the pancreas is found to be enlarged, firm and irregular. Obvious evidences of calcification are often discernible.

The medical *treatment* is directed towards the relief of pain, which should be achieved, if possible, without the use of narcotics because of the tendency to addiction. A bland diet and abstinence from alcohol are basic requirements. If steatorrhœa is present, fat should be restricted and pancreatic extract should be administered in adequate doses. Supplementary vitamins and parenteral protein therapy may be indicated. Surgical procedures required in the management of chronic relapsing pancreatitis range from the elimination of associated disease of the biliary tract to total pancreatectomy. If no associated abdominal disease is demonstrable, medical measures should be given a reasonable trial. If these fail, surgery must be directed towards excision or drainage of pancreatic cysts and the excision of involved portions of the pancreas, if this is considered feasible. The technical hazards of partial or total pancreatectomy in the presence of marked inflammatory reactions are considerable, and they should not be accepted unless more conservative measures have proved ineffectual. It is our feeling that an attempt should be made to relieve the intractable pain of chronic relapsing pancreatitis by unilateral or bilateral extensive splanchnicectomy before radical pancreatectomy is advised.

Pancreatic lithiasis and pancreatic calcinosis are extremely rare, but the symptoms which accompany these pathological states are of such severity as to warrant considerable regard.

The *etiology* is unknown, but the precipitating factors appear to be (1) infection, (2) fibrosis, and (3) obstruction of the pancreatic ducts. It seems reasonable to assume that intraductal calculi may result from simple

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of acute pancreatic necrosis, but the severity of these symptoms is extremely variable, and it is not unusual to encounter large inflammatory cysts in patients in whom the acute attack was not devastating. Symptoms referable to the cysts include abdominal pain, dyspepsia, fullness, tenderness and occasionally back pain. The physical findings, with the exception of the palpable, relatively fixed mass, are meagre. Radiological studies are often helpful. A flat plate of the abdomen may reveal a cystic mass in the region of the pancreas. Skiagrams following a barium meal may delineate more precisely a retrogastric mass or widening of the duodenal sweep.

The *treatment* of inflammatory cysts of the pancreas is essentially surgical, although it is true that some of the smaller pseudocysts will be absorbed spontaneously. When operative measures are decided upon, several procedures are available. Marsupialization of the cyst of inflammatory origin will be effective in many instances, particularly if the cyst is operated on before the walls have become rigid and epithelialized. This simple manoeuvre will often fail, especially if major ductal channels proximal to the cyst are occluded. Failure will be followed by re-accumulation of the cystic fluid or by a persistent external fistula. More definitive measures include: (1) excision of the cyst, which is often impossible when the surrounding inflammation is marked; (2) resection of the cyst along with the involved portion of the pancreas; (3) pancreato-duodenectomy when the cyst involves the head of the organ and closely simulates malignancy; or (4) anastomosis of the cyst to the stomach or jejunum.

Case 4.—A woman, thirty years of age, came to the clinic in April 1947, complaining of pain in the left upper part of the abdomen. The pain was recurrent, and was accompanied by nausea and vomiting. In August 1946, following an acute abdominal disease, a mass appeared in the epigastrium. At operation elsewhere, a pancreatic cyst was found and marsupialized. She remained well for five months, but the attacks of pain then recurred.

A firm, tender cystic mass was palpable in the left upper quadrant of the abdomen. In July 1947, the patient was operated on again and a large cyst involving the body and tail of the pancreas was exteriorized. Drainage persisted intermittently until October 1947, when splenectomy and resection of the body and tail of the pancreas were performed.

Comment: This case demonstrates the ineffectiveness of simple marsupialization in this instance. One attempt at exteriorization was followed by a recurrent cyst, and the second attempt resulted in a persistent fistula. Radical resection of the involved pancreas eliminated the disease.

PANCREATIC TRAUMA

Accidental trauma to the pancreas is uncommon. Non-penetrating wounds occasionally result in pancreatic hæmorrhage, which may be followed by a pseudocyst or fistula. It is reasonable to bear in mind the possibility of pancreatic injury in crushing wounds of the upper abdomen, particularly when the injury is followed within a few days by the appearance of an epigastric mass. Penetrating and gunshot wounds may involve the pancreas, but rarely without being masked by injuries to adjacent viscera. The most

obstruction of the duct, followed by stagnation, infection and alteration in the chemical composition of the pancreatic secretion, leading to precipitation of calcium salts. Pancreatic calcinosis, on the other hand, involves the parenchyma as well as the ducts and must be preceded or accompanied by varying degrees of pancreatic necrosis. It is best, perhaps, to regard pancreatic calculi and pancreatic calcification as advanced reflections of chronic, relapsing pancreatitis, which in turn follows repeated attacks of acute pancreatitis. The microscopic study of the pancreas in these cases reveals a varied picture of involvement, including areas of chronic pancreatitis, calcification, sclerosis of the islands of Langerhans, subacute and acute necroses, and cystic dilatations.

The *symptoms* are similar, of course, to those of chronic relapsing pancreatitis with the important exception that they tend to be more constant, although the victims do have periods of freedom from pain. Mild or latent diabetes accompanies pancreatic calcification in a significant number of cases. The diagnosis is made by radiological study of the abdomen, which reveals the radio-opaque stones in the region of the pancreas. They occur most often in the head and body of the gland.

The *treatment* is surgical. Occasionally, intraductal stones may be removed, but more often the involved portion of the gland must be resected, or the pain must be relieved by extensive sympathectomy.

Case 3.—A male, thirty-nine years of age, was first examined at the clinic in May 1946, complaining of recurrent bouts of abdominal pain. The attacks of pain varied in intensity from a dull ache to severe stabbing distress and were prone to occur following his frequent episodes of alcoholic excess. The pain radiated to the back and was accompanied by anorexia, nausea and vomiting. He had lost 28 pounds in weight.

Abdominal examination demonstrated a large irregular, tender mass in the epigastrium. X-rays of the abdomen revealed mottled areas of irregular density in the region of the pancreas. Glucose tolerance studies demonstrated diminished tolerance characteristic of latent diabetes. At operation a large cyst was found in the head of the pancreas, associated with marked fibrosis and scattered areas of calcification in the remaining portion of the gland. The cyst was marsupialized and continued to drain for six weeks. The pain was relieved temporarily and the patient gained 30 pounds in weight. In the spring of 1948 the pain recurred with increasing severity, and in July 1948 a pancreato-duodenectomy was performed, resecting the head and part of the body of the pancreas. The postoperative recovery was without incident and the pain has been relieved.

Inflammatory cysts occur as a sequel to acute pancreatic necrosis in approximately 10 per cent. of cases. They are, in truth, pseudocysts which are not necessarily confined to the substance of the pancreas and generally lack an epithelial lining. The contents vary from clear fluid to hæmorrhagic debris. They are usually limited to the confines of the lesser peritoneal sac, but since they result from an inflammatory reaction in the retroperitoneal space, they may spread by peripheral expansion to any part of the abdominal or pelvic cavity and may present bizarre clinical patterns. Since they accompany severe degrees of pancreatic necrosis, inflammatory cysts are often associated with mild diabetes.

Pancreatic pseudocysts of inflammatory origin are preceded by symptoms

peated examinations, it is perhaps reasonable to resect the tail and body of the gland in the hope of removing a deeply seated, non-palpable tumour. Total pancreatectomy has been advocated, but this radical manœuvre should not be resorted to unless all other methods of management have failed. Because of the frequency of malignancy in these tumours, wide excision should be practiced.

Case 6.—A woman, thirty-five years of age, complained of recurrent attacks of dimness of vision, followed by disorientation, aphasia and stupor, persisting from thirty minutes to several hours. They came on during periods of hunger and were avoided or minimized by frequent eating. Repeated blood sugar determinations varied from 66 to 35 mg. per 100 ml. At operation an islet cell adenoma, 1.5 cm. in diameter, was found. Resection of the involved portion of the pancreas, including the tumour, resulted in cure.

Pancreatic cysts, other than those of congenital, inflammatory or traumatic origin as previously described, include retention cysts and cystadenomas. Retention cysts derive from obstruction of the pancreatic duct, smaller ducts or acini. They are insidious in onset and often do not cause any symptoms until they attain sufficient size to exert pressure on adjacent viscera. They represent the largest of all pancreatic cysts and may appear as solitary or multilocular structures. Because of the relative freedom from associated inflammatory reaction, retention cysts can usually be excised completely.

Cystadenomas are true proliferative tumours of undetermined origin. They are extremely uncommon. They are irregular, lobulated and multilocular. The cystic spaces are numerous and contain thin, turbid, hæmorrhagic or viscid material. Vague, progressive symptoms, including epigastric pain, fullness and anorexia, occur. The mass may be palpable when the cysts are large.

Papillary cystadenocarcinomas, which may or may not arise from benign cystadenomas, are easily confused with benign cysts in that their symptomatology and gross appearance may be indistinguishable.

Each of these lesions should be completely excised, since the multiplicity of the cystic cavities and the malignant nature of the cystadenocarcinomas do not lend themselves to less radical surgical procedures.

CARCINOMA OF HEAD OF PANCREAS

Carcinoma of the pancreas and of the ampulla of Vater represent approximately 2 per cent. of all carcinomas. Malignant lesions of the head of the pancreas and the ampulla of Vater exhibit many clinical features in common, but they may be differentiated in many instances by a careful analysis of the historical data. Carcinomas affecting the body and tail of the pancreas are vague in the clinical delineations, and the diagnosis, particularly in the early phase of the disease, is very elusive. Carcinoma of the pancreas may arise in the ductal or acinar elements of the gland or in the islet cells, as previously described. Contiguous extension and metastatic spread of the tumour are more rapid in carcinoma of the pancreas than in ampullar lesions.

common injuries to the pancreas are surgically inflicted, during procedures involving the stomach, duodenum, biliary tract or spleen. The mobilization of the duodenum in the removal of a posterior penetrating ulcer may be attended by injury to the pancreas. By and large, these injuries involve only minor ducts and result in transient fistulæ, but occasionally the main pancreatic duct may be injured or divided, with alarming consequences, unless the injury is immediately recognized and repaired. Injury to the tail of the pancreas during splenectomy is less disastrous and more easily avoidable, but may contribute to sub-diaphragmatic accumulations or temporary pancreatic fistulæ.

Case 5.—A young man, eighteen years of age, was seen in the clinic in January 1936. He had been kicked in the abdomen two months before his examination here. At abdominal exploration performed elsewhere two days after the injury, a hæmorrhagic mass was found in the lesser peritoneal sac. A drain was inserted and the fluid which escaped proved to be pancreatic juice. The persistent fistula failed to respond to conservative measures and was anastomosed to the upper jejunum, with entirely satisfactory results.

TUMOURS

Islet cell tumours of the pancreas may be either benign or malignant. Hyperinsulinism may or may not accompany either type.

The *clinical manifestations*, which may begin insidiously, are those of severe hypoglycæmia. The initial symptoms of nervousness, tremor, giddiness and emotional instability may arouse no unusual suspicion on the part of the physician. The later development of severe mental disturbances, including agitation, confusion, coma or convulsions, associated with marked perspiration, may suggest the possibility of hypoglycæmic shock, particularly if the patient relates these symptoms to periods of fasting and hunger. The demonstration of severe hypoglycæmia during a typical attack followed by the dramatic relief of the symptoms by the administration of glucose, by mouth or vein, is essential to the clinical diagnosis. Between attacks the blood sugar values and the glucose tolerance curves may be entirely normal. Efforts to demonstrate the severe hypoglycæmia characteristic of the attacks may require long periods of fasting on the part of the patient. Once the typical symptoms of the disease have been correlated with a demonstrable blood sugar below 50 mg. per 100 ml. and the symptoms have been relieved by the administration of glucose, it must be proved that the hypoglycæmia is not caused by hepatic or adrenal insufficiency. Efforts to control the hypoglycæmia by dietary means should be pursued when the triad of Whipple, i.e., (1) clinical manifestations of severe hypoglycæmia, (2) blood sugar value below 50 mg. per 100 ml. during an attack, and (3) dramatic relief of symptoms by the administration of glucose, is not fully satisfied.

The *treatment* of islet cell tumours is surgical. These tumours are characteristically small and their discovery at operation may be extremely difficult. They may be multiple. They are more prone to occur in the tail and body of the gland, but they may be located in any portion. The ideal surgical procedure is excision of the tumour. If no tumour is revealed after careful re-

fatigability and vague upper abdominal distress and belching. Six months later he began to have intermittent diarrhoea of bulky, fatty stools and generalized pruritus. Loss of weight became prominent at this time. Two months later progressive jaundice and anorexia appeared.

The patient was deeply jaundiced and showed evidence of great weight loss. The liver was considerably enlarged and his gall-bladder was distended and palpable. The hæmoglobin value was 12.5 g. per 100 ml. of blood. The bilirubin was 16 mg. A diagnosis of carcinoma of the pancreas was made. A two-stage pancreato-duodenectomy was performed. The pathological diagnosis was carcinoma of the pancreas. The postoperative course was uneventful.

Results of pancreato-duodenectomy.—During the period from August 1942 to August 1948, 165 patients with carcinoma in the pancreas or ampullar region were examined at the Lahey Clinic. Fifty-six of these were submitted to pancreato-duodenectomy. In addition, 5 patients with benign lesions in this location also had the duodenum and the head of the pancreas resected.

In 56 resections performed for malignant disease there were 8 postoperative deaths, a percentage mortality of 14.3. The composite mortality rate in 61 resections, including 5 benign lesions, was 14.8 per cent. The operative mortality in 20 resections for carcinoma arising in the ampulla of Vater was only 5 per cent., whilst in 30 resections for carcinoma of the head of the pancreas the mortality was 16.7 per cent.

The entire series of 48 patients surviving radical resection for malignant disease of the ampulla or pancreatic head has been followed. Twelve survivors have been followed for five years or more and of these: three, or 25 per cent., each of whom had carcinoma of the ampulla of Vater, are living and well. Six, or 50 per cent., of the original 12 patients who recovered from the operation lived three years or longer. Of 25 immediate survivors of resections performed for carcinoma arising in the head of the pancreas, 18 have since died of recurrence, with an average salvage span of eleven months. Seven are living and well, and one of the seven has now survived forty-three months.

SUMMARY

A number of lesions of the pancreas of surgical interest have been reviewed. Methods of management have been discussed. The results of radical pancreato-duodenectomy have been recorded.

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Malignant tumours of the pancreas affect men more often than women and are most prone to occur in the fifth and six decades.

The *symptoms and signs* of carcinoma of the pancreas are *insidious* in onset unless the lesion arises near the common duct, in which location the symptoms may progress rapidly. Abdominal pain is the most common symptom of carcinoma of the pancreas. The pain is usually dull and aching in character and is referred to the back. It is more pronounced at night and may be partially relieved by sitting in an attitude of flexion. Colicky pain, radiating to the right scapula, is common enough to confuse the disease with cholelithiasis. Rhythmic pain, not unlike that of ulcer distress, may be an early indication of malignant disease of the pancreas. Weight loss is exceedingly common and may be rapid and extreme. It is often the most prominent symptom of the disease. Jaundice, of a persistent, progressive nature, is a cardinal symptom and sign of malignant tumours of the pancreas, but contrary to repetitive comment in the literature, the jaundice is seldom painless. Diarrhoea and steatorrhoea, a reflection of ductal obstruction, occur in a significant number of cases. Constipation is similarly observed. Weakness, anorexia, nausea and vomiting are frequent accompaniments. Jaundice associated with a demonstrable enlargement of the liver is usually present. A distended gall-bladder is palpable in 50 to 75 per cent. of cases. Tenderness over the pancreas is uncommon, and a palpable tumour is present only in the far advanced cases.

Positive laboratory data are meagre, apart from elevation of the serum bilirubin, which parallels the clinical jaundice. From 20 to 30 per cent. of patients with carcinoma of the pancreas show derangements in glucose metabolism if careful studies are made. Undigested meat fibres in the stool occur when ductal obstruction is marked. Reduction in the pancreatic enzymes, as determined by analyses of duodenal contents, is a more direct but more difficult means of demonstrating pancreatic insufficiency.

Radiological studies in detection of pancreatic carcinoma are indirectly revealing by eliminating other sources of gastro-intestinal disease. Occasionally an enlarged pancreatic head can be presumed on the basis of a demonstrable widening of the duodenal sweep.

The accuracy in diagnosis of carcinoma of the pancreas and ampulla of Vater is low. This inaccuracy in clinical recognition is, to some degree, inherent in the nature of the disease, and reflects the fact that the diagnosis must be pursued by a process of deduction and elimination. Yet the percentage of accuracy in clinical detection can be improved by discarding the classical concept that the disease is manifested by painless jaundice and accompanied by a palpable, distended gall-bladder (which combined features are present in only 25 per cent. of cases). The importance of demonstrating alterations in carbohydrate metabolism and deficiency in pancreatic enzymes in duodenal contents must be borne in mind.

Case 7.—A male, sixty-six years of age, was first seen in the clinic in September 1948. He was well until one year before admission, when he first noted easy

more exact bilirubin estimation which may be useful in special circumstances. It can, however, be very misleading unless hæmolysis of the specimen is prevented, although Neuberger's³ modification is a safeguard in this respect. By this method normal limits are from 1 to 5 and carotin is the only pigment likely to interfere. In the detection of latent jaundice, Fouchet's⁴ qualitative test is almost as good as the icterus index and uses less material. A positive Fouchet's test indicates an abnormally high serum bilirubin concentration.

Tests for bile pigment in urine.—Clinical tests for urinary *bilirubin* are very insensitive, but with suitable techniques the detection of traces of bilirubin can be of great significance. Either the Harrison-Fouchet test⁴ or the less specific methylene blue test⁵ may be used. These tests are positive very early in hepatitis and are of value in the pre-icteric stage. They may also be positive in non-jaundiced cases of hepatic cirrhosis. The classical absence of bilirubinuria in hæmolytic jaundice is also noteworthy, although secondary liver damage may upset this finding.

Urobilin and *urobilinogen* have the same clinical significance, the latter changing to the former on standing, but it is more convenient to test for urobilinogen on a fresh afternoon specimen of urine by the method of Watson and others⁶. This may easily be made a semi-quantitative procedure when the results are expressed in Ehrlich units (normal 0 to 1).

Although the presence of urobilinuria constitutes a very sensitive test of the excretory function of the liver, the test is paradoxically negative in *complete* biliary obstruction because no urobilinogen can then be formed from bilirubin in the gut. It is a particularly valuable indicator of liver damage in the absence of clinical jaundice, e.g., in cirrhosis, pre-icteric hepatitis or liver abscess. It may be positive in heart failure or in any severe general infection.

In the presence of jaundice, interpretation is much more difficult. Results are typically negative in uncomplicated biliary obstruction and are usually positive in jaundice due to cirrhosis, hepatitis, or hæmolysis. There are, however, many exceptions, and possibly the only safe generalization would be that the presence of urobilinuria is incompatible with complete biliary obstruction; it certainly does not rule out a partial obstruction. On the other hand, the absence of urobilin from the urine would be against a diagnosis of cirrhosis.

*Bromsulphthalein test*⁷.—This dye is excreted mainly in the bile; it is injected intravenously and the fraction remaining in the circulation after a given time is determined. With a dose of 2 mg. per kg. the dye should have left the circulation completely in 20 minutes, and with 5 mg. per kg. the appropriate time is 30 minutes. The larger dose leads to greater sensitivity, but to occasional reactions.

This test has been widely used in America and appears to be a valuable procedure in non-jaundiced patients, being about as sensitive as the intravenous hippuric acid or the cephalin-cholesterol tests⁸. It is often positive

TESTS OF LIVER AND PANCREATIC FUNCTION

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THIS title includes a large number of procedures some of which are more closely related to liver function than others. There is probably none which tests liver function and nothing else, and some of the most useful of the newer tests do not depend upon any known function of the liver and must be regarded as partly empirical. The great sensitivity of many of the tests means that we must be prepared to distinguish between primary liver damage and secondary involvement which may occur in heart failure, anæmias, and in certain acute and chronic infections. It is impossible within the scope of this article to mention every test which has been proposed, but those in most general use may be classified as follows.

TESTS DEPENDING MAINLY UPON BILIARY EXCRETION

The tests in this group are of particular value in patients not obviously jaundiced. The serum bilirubin estimation is also important in providing a record of the intensity of jaundice when present, and the proportion of direct bilirubin is helpful in distinguishing hæmolytic jaundice from the other types. These tests, however, usually fail to distinguish jaundice due to hepatitis from that due to biliary obstruction.

Serum bilirubin estimation.—The photo-electric method of Malloy and Evelyn¹ appears to be the method of choice, and gives a separate estimation of "direct" and "indirect" bilirubin.

The normal limits for total bilirubin may be taken as from 0 to 1 mg. per 100 ml., values between 1 and 3 indicating latent jaundice. This is often an important finding in conditions such as hepatic cirrhosis, subclinical hepatitis, and in the hæmolytic anæmias. If jaundice is present, a high proportion of indirect pigment indicates the hæmolytic or retention type. Thus if more than half the pigment is indirect, a hæmolytic jaundice is probable^{1,2}. If, on the other hand, the pigment is mainly direct, the result is of less help in differential diagnosis.

In the older and less precise terminology, a preponderance of direct pigment corresponds to a "prompt" or "biphasic" Van den Bergh reaction: a preponderance of indirect pigment to a "delayed direct" or a "positive indirect" reaction. These terms, however, are probably better avoided, as they are difficult to define unequivocally and are a frequent source of confusion.

Icterus index and Fouchet's test.—The icterus index is a substitute for the

results in the former group were four cases of infective hepatitis in young adults from the Services, a class of patient in whom liver function is no doubt above average. Impaired tolerance in obstructive jaundice usually

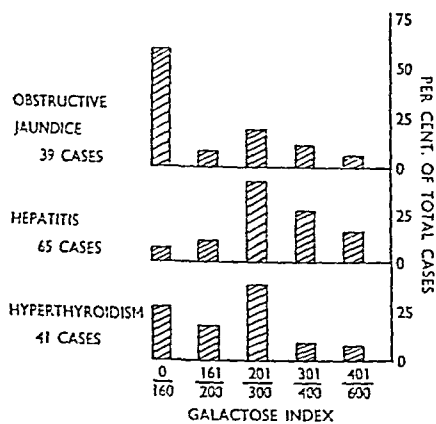


FIG. 1.—Galactose index.

occurs after the first three weeks, after repeated attacks of obstruction, or with complications such as cholangitis. The test is therefore of some value in distinguishing these two groups, if interpreted with due regard to clinical data. Results are above normal in a high proportion of cases of hyperthyroidism¹³, in which condition the test has diagnostic value. Here, increased intestinal absorption perhaps contributes to the impairment of tolerance¹⁴, although this has been denied by Moseley and Chornock¹⁵. Infections and heart failure may

also cause some impairment of tolerance.

The intravenous modification gives statistically similar results in jaundiced patients. Thus in the series of Bassett and others¹⁴, about 80 per cent. of the obstructive cases were below, and 80 per cent. of the toxic and infective cases above, the 20 mg. 100 ml. level at 75 minutes. Results are mainly negative in hyperthyroidism. The preparation and injection of the 50 ml. of galactose solution is a technical drawback, but the test has the advantage of avoiding inequalities in absorption rate.

Lævulose tolerance tests.—Although the theoretical basis of this test has been criticized by Mann¹⁶, recent modifications based on blood lævulose determinations have yielded results of clinical interest to a number of workers. For details the original papers should be consulted^{17 18 19 20}.

Serum protein estimation.—Chemical methods are adequately described in current textbooks.

In cirrhosis and subacute hepatitis the albumin (normal 4 to 5.5 g. per 100 ml.) tends to be reduced, and the globulin (normal 1.5 to 3.0 g. per 100 ml. raised, whilst the total protein (normal 6 to 8 per cent.) may be high, low or normal. In acute hepatitis about half the cases show similar, although usually less striking, changes. In hepatic carcinomatosis such alterations are minimal or absent. The estimation may therefore be of diagnostic value, particularly in chronic cases. The serum albumin is also of prognostic importance in subacute and chronic hepatitis, figures below 2 g. per 100 ml. indicating a poor outlook²⁰.

Neither of these findings is a specific indication of liver damage. Hyperglobulinæmia can occur in most chronic infections and is particularly striking in lymphogranuloma, kala-azar, and multiple myelomatosis. Hypoalbuminæmia is common in nephritis and in malnutrition from any cause. Nevertheless, a combination of these two alterations is typical of chronic hepatitis and affords valuable confirmatory evidence of the condition.

in "chronic low-grade illness", and the results may be partly influenced by the activities of the reticulo-endothelial system. Bromsulphthalein has been difficult to obtain in this country since 1939. The principal value of this test is in the confirmation of liver involvement in the non-jaundiced patient, and it has found considerable application in conditions such as cirrhosis and non-icteric hepatitis.

Fæcal urobilinogen estimation.—Although not exactly a liver function test, this estimation is important in the investigation of hæmolytic jaundice, in which condition the normal stool pigment is present in grossly increased amounts. Normal values are from 30 to 220 mg. per 100 g. of stool⁹, and values of as high as 1000 to 2000 may occur in hæmolytic jaundice. Such stools are normal in appearance and the estimation is therefore of value in diagnosis.

TESTS MAINLY INDEPENDENT OF BILIARY EXCRETION

*Hippuric acid test*¹⁰.—This convenient test depends upon the rate of hepatic synthesis of glycine. However, the conjugation of glycine with benzoic acid occurs in the kidney as well as in the liver and results are therefore affected by renal damage, if present. Oral and intravenous modifications are available, and the latter is the more sensitive⁸.

In the oral method the patient should excrete more than 3 g. of hippuric acid, and in the intravenous method more than 0.7 g. (both expressed as benzoic acid).

The test appears to have found its best applications in the detection of liver damage in non-jaundiced patients, e.g., during anti-syphilitic treatment and in recovering hepatitis. Positive results are frequent in hyperthyroidism and in many acute and chronic infections, as well as in all types of gross liver disease. In obstructive jaundice the test has been used in a prognostic sense, and in this condition an excretion of less than 2 g. (oral method) is said to indicate a poor operative risk. The test is of limited value in the investigation of jaundice of unknown origin because uncomplicated biliary obstruction rapidly leads to results quite as low as those seen in toxic and infective jaundice. Whether this is due partly to associated renal damage has not been definitely determined.

Galactose tolerance tests.—Recent modifications rely entirely upon blood galactose determinations.

In the oral method¹¹ a dose of 40 g. of galactose is administered and the subsequent blood galactose levels should not exceed 80 mg. per 100 ml. The sum of the half-, one-, one-and-a-half-, and two-hourly values, expressed in the same units, is called the galactose index and should not exceed 160. In the intravenous method 25 g. of the sugar are given and the blood should be free of galactose two hours later¹².

I have had most experience with the galactose index. Some typical results with this test are shown in fig. 1. Results are usually above normal in infective hepatitis, cirrhosis, and post-arsphenamine jaundice (89 per cent.), and are often normal in obstructive jaundice (59 per cent.). The only normal

post-arsphenamine jaundice and Weil's disease were positive. On the other hand, only 14 per cent. of cases of obstructive jaundice gave positive

reactions, and none gave strongly positive tests. A proportion of patients with heart failure, pernicious anæmia, and chronic infections also gave positive results, which were particularly frequent in rheumatoid arthritis. The test appears to be of definite value as a general indicator of liver dysfunction and in the differentiation of obstructive from non-obstructive jaundice. Its value in jaundice is increased by

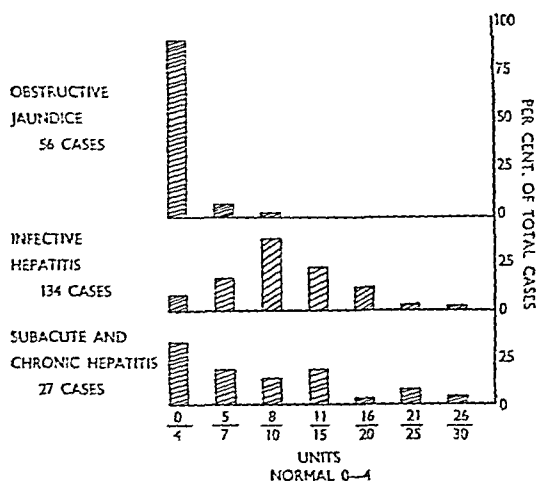


FIG. 2.—Thymol turbidity.

combination with the serum alkaline phosphatase estimation, as indicated below.

Cephalin-cholesterol test²⁸.—This test has been widely used in the United States and appears to give somewhat similar results to the gold reaction. The preparation of the cephalin is a technical obstacle, and the results depend to some extent upon the age and source of the cephalin. Opinions are divided as to its value in distinguishing obstructive from non-obstructive jaundice²³. Results are usually positive in cirrhosis and in infective hepatitis, and often remain positive for long after the disappearance of jaundice²⁹.

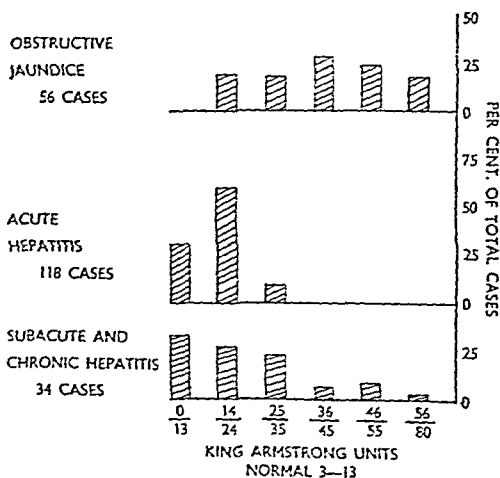


FIG. 3.—Serum alkaline phosphatase.

The thymol test³⁰.—In this test the result may be recorded as a turbidity (normal 0 to 4 units) or as a flocculation, and the latter appears to be rather more sensitive and selective. Typical results for the turbidity test are shown in fig. 2. As with the gold tests, results are usually positive in infective hepatitis (91 per cent.)

Plasma prothrombin estimation.—The prothrombin index of Quick²¹ gives the plasma prothrombin concentration as a percentage of normal. Although not exactly a liver function test, this estimation is important in surgical cases of jaundice. Reduced values imply a definite risk of hæmorrhage and are a strong indication for vitamin K therapy. Prothrombin response to vitamin K has also been used as a liver function test; a failure of a low prothrombin index to respond to parenteral vitamin K therapy means gross liver damage. The use of the test in this way is, of course, confined to those cases in which plasma prothrombin is low before treatment—about 25 per cent. in Stein's series of jaundiced patients²². In such cases the failure to respond would suggest hepatitis rather than biliary obstruction as the cause of jaundice, and would, in any case, usually contraindicate operation.

EMPIRICAL TESTS

Although these tests are among the most valuable at present available from the diagnostic standpoint, they depend upon chemical and physiological mechanisms not yet fully elucidated. Two types of test will be considered.

First, there are the flocculation tests, which have been shown to depend mainly upon changes in the serum gamma globulin, which is probably produced in excess by the liver in certain pathological states. Of these the Takata-Ara and the formol gel tests were the earliest representatives, but have been largely superseded by the cephalin cholesterol, the serum colloidal gold, and the thymol tests. I have recently reviewed the relative merits of these tests²³. They all show a high proportion of positive results in most types of hepatitis, although they are not specific for this condition, since gamma globulin may also be produced by other parts of the reticulo-endothelial system in certain acute and chronic infections.

Secondly, there is the serum alkaline phosphatase estimation. The concentration of this enzyme is mainly increased in cases of obstructive jaundice. This test is also not specific for liver involvement, as increases occur in infancy and in many bone diseases.

Takata-Ara reaction.—This was the first of the flocculation tests to achieve popularity for the detection of cirrhosis, but it has to some extent been superseded by later procedures. The extensive literature was reviewed by Magath²⁴. The principal objections are the lack of standardization of the many different techniques employed and the frequency of "false positive" results in chronic infections. It does not appear to be of proved value in differential diagnosis in jaundice, although there is undoubtedly a statistical difference between the results in obstructive and infective jaundice which some workers have found useful²⁵. It would be safe to say that negative results are unusual in hepatitis.

Serum colloidal gold reaction.—This was introduced by Gray in 1940 in a form technically difficult to standardize²⁶. The modifications of MacLagan²⁷ are more suitable for routine work. Results were mainly positive in infective hepatitis (92 per cent.) and cirrhosis (81 per cent.). About half the cases of

as high as in biliary obstruction. The test may therefore be difficult to interpret by itself, but becomes of more value when combined with the flocculation tests.

COMBINATION OF TESTS

It is generally agreed that no one test gives a satisfactory picture of the multiple functions of the liver, and it is usual to do several tests when possible. The serum alkaline phosphatase and the flocculation tests form a particularly valuable combination in jaundice as they have opposite tendencies in obstructive and non-obstructive types.

Thus in a series of 200 cases recently collected³² this distinction could be made in 79 per cent. of cases with the aid of the phosphatase and thymol flocculation tests. All cases of jaundice with 0 or 1+ flocculations plus a phosphatase of over 35 units were obstructive; all cases with normal phosphatase levels or with thymol flocculation above 1+ were non-obstructive. A residual group gave equivocal results (21 per cent.). These results are illustrated graphically in fig. 4, where the shaded area represents the equivocal results.

DISCUSSION

The interpretation of any test or combination of tests must always depend partly upon clinical data because of the possibility of secondary hepatic damage in diseases not primarily involving the liver, and because of the non-specific nature of some of the tests employed. It is, however, not unreasonable to claim that a suitable combination of tests can often give the clinician definite help in the diagnosis and prognosis of liver disease. The choice of test depends to some extent upon the sort of information required, which varies in different cases. Three typical types may be taken for discussion.

Jaundice of unknown origin.—This is the most difficult type, and there is probably no test which will give a definite answer in every case. Tests showing a maximum difference between the obstructive and the toxic and infective groups are the flocculation tests, the alkaline phosphatase, and galactose tolerance, arranged in order of preference. The serum protein and urine urobilin tests also show a statistical difference in the two groups, but the degree of overlap is greater. A combination of the thymol flocculation test and the alkaline phosphatase estimation is probably the most practical procedure at present available, as it may be carried out on a single blood specimen and appears to differentiate between the two groups in about 79 per cent. of cases, as shown above. The galactose index is of some value in difficult cases, particularly when normal tolerance is found in a middle-aged patient, which is very unlikely in the presence of hepatitis or cirrhosis.

Jaundice of known origin.—Here help is needed in prognosis and in estimating operative risk, and for these purposes the hippuric acid test and the serum protein estimation have been most used. In surgical cases the prothrombin determination, although not exactly a liver function test, is obviously of paramount importance in relation to the risk of hæmorrhage.

Suspected liver disease without clinical jaundice.—In this group any test

and cirrhosis (67 per cent.), and mainly negative in obstructive jaundice (92 per cent.). Similarly, only about half the cases of post-arsphenamine jaundice were positive. The thymol flocculation test is one of the most sensitive tests available in convalescent hepatitis, often remaining positive some weeks or months after the other tests have become negative²⁹. Although not a specific indication of liver damage, this test is less affected by non-hepatic diseases than the gold test, and is a valuable diagnostic aid in liver disease.

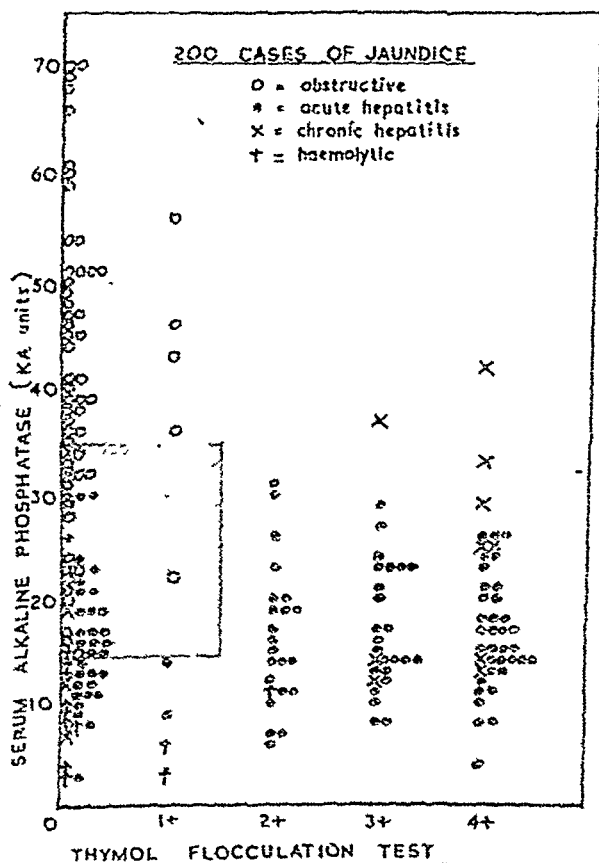


FIG. 4.—Thymol flocculation test.

Serum alkaline phosphatase.—The method of King and Armstrong³¹ is convenient, and results I have obtained with this method are illustrated in fig. 3. Excluding the high values associated with infancy and bone disease, the test is useful in liver diseases because of the high level often found in obstructive jaundice (usually over 35 units). In infective hepatitis, amyloidosis, and liver abscess it often reaches 30 units, and in cirrhosis may be

The test is positive if the pupil on the treated side is dilated as compared with the other pupil five minutes later. Opinions vary as to the value of this test, which is probably not specific for acute pancreatitis.

(2) *Chronic pancreatic disease*

In these cases more time is available and a larger variety of tests can be employed. The enzyme tests described above are still applicable, but in addition, carbohydrate metabolism can be investigated and evidence sought of impaired digestion and absorption of food.

The enzyme tests on blood and urine are on the whole disappointing in this group, although the serum lipase is claimed to have some advantages. The trypsin content of the duodenal contents is, however, a valuable estimation, and is almost indispensable in the investigation of infantile steatorrhœa, a condition now recognized as having a dual etiology. Some cases are due to cœliac disease and some to a congenital cystic fibrosis of the pancreas; in the latter group trypsin is absent from the duodenal contents. The principal difficulty with this test is concerned with the technique of duodenal intubation. It is essential to obtain an alkaline bile-stained juice for analysis.

Glucose tolerance tests, although often normal, may at times reveal impairment of tolerance due to deficient insulin production. This is particularly likely in the cases with pancreatic calculi, a fair proportion of which exhibit diabetic manifestations. Although much of the pancreas can be destroyed without interfering with glucose tolerance, the test is nevertheless worth doing in adult cases of steatorrhœa in which a pancreatic lesion is suspected, since the typical curve in the idiopathic steatorrhœa group is abnormally flat and is therefore the exact opposite of that expected in pancreatitis.

Stool microscopy may reveal evidence of inefficient digestion of various types of foodstuff. Thus, fat globules, fatty acid crystals, striated muscle fibres, and occasionally starch granules may be seen. In pancreatic disease, fat globules and striated muscle fibres are the important findings, indicating deficient secretion of lipase and trypsin respectively. It is important to be sure that the patient is taking some meat in the diet, and that liquid paraffin has not been administered.

Fæcal fat estimations give a more sensitive indication of inefficient fat digestion, and in pancreatic disease an increase in the neutral unsplit fats is the expected finding. However, in infants much fat splitting may occur by bacterial action and the differentiated estimation is not so reliable.

Normal values for total fat are up to 25 per cent. of the dry stool weight, and of the total fat not more than 25 per cent. should be unsplit. This figure may be altered to 33 per cent. for infants on a milk diet. If the total percentage is low, however, the degree of splitting is unimportant.

Fat balance experiments represent the latest contribution to this subject, and undoubtedly give more information than a simple fæcal fat estimation.

For this test the patient must be admitted to hospital and the services of a dietitian are essential. The balance is usually estimated over a four-day period with a fat intake of 50 g. per day. Normal subjects absorb more than 90 per cent. of the fat

may sometimes give useful information, and the serum bilirubin and urine urobilin tests are the easiest to carry out; the former, however, will often give negative results in cases with obvious liver damage. The bromsulphthalein test is perhaps more sensitive. The flocculation tests are of particular value in the detection of cirrhosis, and the phosphatase in cirrhosis, amyloidosis, and liver abscess. As confirmatory tests, galactose tolerance, hippuric acid and serum proteins may be valuable in special cases.

CHOICE OF TESTS

It will be evident from the above that it is impossible to make any general recommendations as to the "best" liver function tests, since the different tests have different indications and advantages. Although it is impracticable to do all these tests on every patient, there is no doubt that a combination often yields more information than any one test. My present preference is to do the serum bilirubin, thymol, gold, phosphatase and urine urobilinogen tests as a routine, and to reserve the others for special cases. These five tests appear to be sufficiently sensitive to detect most types of liver damage, and will usually distinguish obstructive from non-obstructive jaundice.

TESTS OF PANCREATIC FUNCTION

Tests applicable to acute pancreatitis are in general quite different from those suitable for chronic pancreatic disease, and it will therefore be useful to divide them into two groups.

(1) *Acute pancreatic necrosis*

This condition constitutes an acute surgical emergency and therefore only fairly simple tests which can be carried out rapidly are of value. These consist mainly in estimation of pancreatic enzymes in the body fluids, and of these the *urinary diastase* estimation is probably the easiest to perform.

Normal values are up to about 30 Wohlgemuth units in casual urine specimens. Values over 100 are usual in acute pancreatitis, although the figure may fall rapidly to normal after the first one or two days. The same enzyme can be estimated in the serum, giving a normal range of 80 to 150 glucose units³³, with up to 1000 or more units in acute pancreatic necrosis.

Both these estimations can also give raised values if the pancreas is involved in certain other processes, e.g., a peptic ulcer eroding the pancreas. Occasional cases of perforated peptic ulcer without obvious pancreatic involvement may also give high values, presumably from peritoneal absorption of the enzyme. High values are also seen in mumps without pancreatic involvement. However, a very high value in a patient with acute abdominal symptoms is nearly always due to pancreatitis, and in an early case a normal result is against this diagnosis.

Serum lipase and trypsin can also be estimated but do not appear to have any marked advantage over diastase for the present purpose.

Loewi's mydriatic test should also be mentioned. It is performed by placing one drop of 1:1000 adrenaline solution into one conjunctival sac.

PORTAL HYPERTENSION

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ALTHOUGH most of the important aspects of the morbid anatomy of the conditions which give rise to an increased pressure in the portal circulation have been appreciated for many years, the subject has aroused new interest as a result of the achievements of modern surgery of the blood vessels, and a further study has been made, both of this morbid anatomy and of the physiological conditions which govern it. Furthermore, important discoveries of the functions of the plasma proteins and of their elaboration by the liver have helped in forming a prognosis of these conditions and have consequently influenced the choice of treatment.

EXTRA-HEPATIC OBSTRUCTION

By means of direct measurement it is possible, when the abdomen is open at operation, to take readings of the pressure in the portal system: normally this pressure ranges between 60 and 110 mm. of water, but in cases of obstruction readings up to 600 mm. of water may be obtained, and any figure over 150 should be considered as definitely pathological. The obstruction may be due to disease of the liver, "intra-hepatic" obstruction, or it may be "extra-hepatic" due to venous obstruction more peripherally. In this latter case it is most important to determine the site of the obstruction; it may involve the portal vein and thus produce a raised blood pressure throughout the portal drainage area, or it may affect only some of the radicals of the portal system, thus giving rise to a localized portal hypertension. In practice it is found that the great majority of these extra-hepatic portal obstructions are due either to thrombosis in the veins, or to occlusion by malignant growths.

Determination of site of obstruction.—When the block causes generalized portal hypertension all of the portal vein radicals will be engorged, and every available means of collateral circulation will become opened up.

There are four sites where such collaterals occur. The first is in the retroperitoneal tissues, when vessels in the lienorenal ligament, and around the pancreas and retroperitoneal portions of the colon, anastomose with adjacent systemic vessels, including the tributaries of the adrenal and renal veins. At operation in such cases these sites are seen to be occupied by numerous small vascular channels which ooze freely unless special measures are employed to secure hæmostasis. This group of vascular channels is entirely beneficial.

The second group is in the alimentary tract at the upper junction of the systemic and portal circulations in the neighbourhood of the lower end of the œsophagus. Here, in portal hypertension, varicosities develop, at first

ingested³⁴, whilst patients with cœliac disease, sprue, idiopathic steatorrhœa or pancreatitis absorb a diminished proportion down to 50 per cent. or less.

This test will not of course distinguish malabsorption due to idiopathic steatorrhœa from that due to pancreatic disease. It is, however, a more accurate technique than the simple fœcal fat estimation and reveals normal absorption in many cases showing occasional excess of fat in isolated stool specimens. On the other hand, normal stool fat results are usually associated with normal absorption, so that the balance test is mainly indicated in cases with high stool fats.

Fœcal nitrogen estimations can be done as part of the balance procedure and are said to be of help in this connexion. Excretion of more than 15 per cent. of ingested nitrogen usually indicates a pancreatic lesion³⁵.

I am indebted to the editor of the *Journal of Clinical Pathology* for permission to reproduce parts of a previous article, and to the editor of the *British Medical Journal* for permission to reproduce figure 4.

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It is difficult to assess the factors which cause extra-hepatic obstruction to the portal circulation: in children there may have been an extension of the obliterative process from the umbilical vein and ductus venosus to the portal vein, or there may be some congenital abnormality of the portal vein itself. In others, trauma, local inflammation or vascular disease may be predisposing factors. I have recently seen two patients with splenomegaly in whom carcinoma of the stomach had caused obstruction to the splenic vein, so that the presence of a tumour must be carefully excluded.

INTRA-HEPATIC OBSTRUCTION

Intra-hepatic obstruction is occasionally associated with thrombosis of the portal veins in the liver, but practically all cases are due to cirrhosis; this may be a typical Lænnec's cirrhosis, or may follow infective hepatitis or any other condition which causes necrosis of liver tissue. With the increasing prevalence of infective hepatitis this type assumes a greater importance.

DIAGNOSTIC PROCEDURES

The symptoms of portal hypertension are hæmorrhage from the œsophagus or abdominal distension due to ascites. The investigation of a case submitted for consideration with a view to surgical treatment involves verification of the diagnosis and assessment of the general condition, with special reference to the liver function and the danger to life as a result of hæmorrhage. Clinical examination will show enlargement of the spleen, unless the patient has had, as not infrequently happens, a previous splenectomy; the liver is by no means always palpable, and ascites not constant; jaundice usually indicates severe liver damage. Certain special investigations are most valuable:—

Radiological examination of the œsophagus during a barium swallow should be undertaken, varices which appear as irregular rounded filling defects (fig. 1, p. 214) being positive evidence of portal hypertension; in their absence the diagnosis should be in doubt, but an œsophagoscopy may be necessary before their presence can be excluded. Peritoneoscopy is occasionally helpful in order to examine the surface of the liver, and involves little more discomfort to the patient than tapping the abdomen.

An *estimate of liver function* is essential; it is usually more depressed in the cases with ascites but there may be other evidence of liver damage, such as jaundice, which, although not always obvious, is indicated by a raised serum bilirubin level.

It is most important to ascertain that the ascites is the result of the hypertension and not caused by hypoproteinæmia; if it is due to the latter, œdema of the legs will probably be present, but ascites alone, by pressure on the inferior vena cava, may cause such œdema, which will disappear after tapping of the abdomen. Thus an *estimation of the blood proteins* is essential

in the submucosa but later occurring also outside the muscular walls of the œsophagus. In certain cases these submucous varicose veins may extend up as far as the cervical portion of the œsophagus, and they are the cause of hæmatemesis which may be the first warning of the disease, but may also be the cause of a fatal termination.

Patek and others (1948) found in their study of 124 patients with hepatic cirrhosis, that in 42 in whom hæmatemesis occurred it was fatal in 22, and that half of these patients died within one year of the first hæmorrhage.

The third site is at the opposite end of the alimentary tract in the anal canal, where the engorged veins appear as hæmorrhoids, although hæmorrhoids are scarcely more frequent in patients with portal hypertension than in other people of the same age. It is important to look for evidence of portal hypertension in anyone complaining of "bleeding piles", and to avoid local treatment in such cases; it must be very exceptional for dangerous bleeding to occur from this source and local treatment is sure to fail if its purpose is to control the bleeding.

The fourth situation is the anastomosis between portal and systemic circulation along the ligamentum teres in the falciform ligament, the site of the obliterated umbilical vein, giving rise to the "caput medusæ" of dilated veins in the subcutaneous tissue of the anterior abdominal wall. Other attachments of the liver to the parietes share in this anastomosis.

In cases in which there is extra-hepatic portal obstruction of the localized type, it is found in clinical practice that the splenic vein is usually involved. In the alimentary tract, if the obstruction is limited in extent, the normal anastomoses are adequate to provide a collateral circulation, but if the obstruction is more widespread, gangrene of the affected portion of the gut occurs with a rapidly fatal issue.

Predisposing factors.—Many patients with portal hypertension present Banti's syndrome: splenomegaly, anæmia with leucopenia and thrombocytopenia, and hæmatemesis which may be associated either with intra- or extra-hepatic portal obstruction. In the past it was considered that cirrhosis of the liver was an essential feature of Banti's disease, but a small percentage of patients showed no evidence of liver abnormality. Whipple and his associates have demonstrated that in this group the portal obstruction is extra-hepatic, due to a block either in the portal vein itself or in the splenic vein. Such patients will develop a collateral circulation and bleeding from œsophageal varices may prove fatal; it is, however, important in these cases to locate the site of the obstruction, for if it is in the splenic vein, removal of the spleen will relieve the patient of this risk of hæmorrhage, whereas in other cases this danger will persist. Extra-hepatic obstruction should always be considered probable if the liver does not show evidence of cirrhosis at operation, and a careful examination of the portal and splenic veins should be made; if there is doubt, manometric readings should be taken of the pressures in these veins.

the present state of knowledge readings below 2.5 per cent. may be regarded as absolute contraindications for operative measures to relieve the hypertension. Such patients should be treated by other means, for sufficient regeneration of liver tissue occasionally takes place to improve their hepatic function and make them fit subjects for operation at a later date.

SURGICAL INTERVENTION

The aims of surgery in portal hypertension have been to reduce the risk of dangerous hæmorrhage from œsophageal varices, or to relieve ascites. In the past, various surgical methods, either palliative or aimed at reducing the hypertension by providing collateral circulation, have been employed. Some palliative measures have attempted to remove sources of dangerous hæmorrhage; they include injection of sclerosing solution into œsophageal varices, ligation of veins outside the œsophagus by a transthoracic approach, and even œsophago-gastrectomy. It is natural that no lasting claims can be made for such methods. Other palliative operations have attempted to drain away ascitic fluid; for this purpose the renal pelvis or ureter has been implanted into the peritoneum, the saphenous vein has been used in the same way, or buttons have been placed in the abdominal wall to allow the fluid to escape into the subcutaneous tissues; again the results are disappointing, usually because adhesions obstruct any opening which is made.

Indirect methods of improving the anastomosis between the portal and systemic circulation have met with occasional success. Of these the one most commonly employed is the *Talma-Morison operation*, promoting vascular anastomosis through adhesions between the omentum and abdominal wall. This operation has, in some cases, given remarkable results, and still has a place in the treatment of the condition.

Splenectomy alone may in some instances be a palliative operation by diminishing the volume of blood circulating through the portal system; it often gives temporary relief from hæmatemesis, but its real value is in extra-hepatic obstruction involving the splenic vein alone, and here it will be curative. Thus it is important to recognize this small group of cases and refrain from any further operative procedure.

SPLENO-RENAL ANASTOMOSIS

Finally, there is the operation which involves the making of a direct venous channel between the portal and systemic circulations. According to Whipple, early attempts in this direction were made as long ago as 1911, when Gunn, in Ireland, anastomosed the ovarian and superior mesenteric veins; others used the splenic and spermatic veins, or the superior mesenteric and the inferior vena cava. Unfortunately, these venous shunts were very liable to become obliterated by thrombosis and it was not until 1945, when Blake-more and Lord described their non-suture technique using a metal tube,

in these cases. There is often a history of mild dyspepsia, and other symptoms due to deficient liver function may be present.

The serum globulin content is variable, but accurate readings of the *serum albumin* give a fair indication of the degree of liver deficiency; a reading



FIG. 1.—Barium swallow in a case of portal hypertension, showing filling defects due to œsophageal varices.

below 3 per cent. indicates severe liver damage, and in such patients ascites is probably due to the albumin deficiency rather than to portal back-pressure. Such patients do not stand surgical procedures well; unless life is endangered by repeated severe hæmatemesis they should not be operated upon, for they will probably die of cholæmia or mesenteric thrombosis. In

CHOLECYSTOGRAPHY

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As the signs and symptoms of gall-bladder disease are often vague and even on occasions misleading, it is now well realized that investigation of a patient with upper abdominal symptoms is not complete without cholecystography. Indeed, in many centres, especially in the United States, cholecystographic and gastro-intestinal examinations go hand in hand. Indication for one examination is regarded as an indication for both methods. In this country, the advisability of carrying out full gall-bladder investigation when symptoms are not characteristic, and when the gastro-intestinal examination gives negative results, is realized. The examination is useful also in the elucidation of tumours and masses of indeterminate origin in the epigastrium and right upper abdomen, even when they prove to be extra-biliary, e.g. hepatic and biliary cysts, pancreatic, suprarenal and renal masses, and other more rare causes of tumour. Evidence of past or present cholecystitis is found in 60 per cent. of autopsies, and gall-stones in 6 to 10 per cent., increasing up to 25 per cent. in subjects over sixty years of age (Newell, 1948).

METHOD OF EXAMINATION

A preliminary film of the abdomen must be taken to decide if opaque calculi are present, as these may be largely hidden later by the dye, especially where calcification is rather faint. The gall-bladder may be anywhere from within the liver to below the iliac crest. It has also been recorded as lying in the left half of the abdomen. Of recent years sodium tetraiodophenolphthalien (S.T.I.P.P.) has been gradually replaced by the newer dye, β -(4-hydroxy-3:5-di-iodophenyl)- α -phenyl-propionic acid, which was introduced by Dorhn and Diedrich in 1940. This drug is known as "pheniodol" in this country and as "priodax" in America. It can be administered as a powder, granules or tablets, but not intravenously, as it produces convulsions if injected into the veins. The dose is 3 g. and can be increased to 6 g. if thought necessary, but as the dose increases so are the reactions apt to increase. The symptoms of nausea, vomiting and diarrhoea are much less frequent and less severe than with S.T.I.P.P. Pheniodol may produce tingling or burning of the mouth or throat and occasionally burning micturition, but these effects are transitory and are seldom severe.

Routine examination consists of:—

(1) Adequate alimentary preparation, chiefly by the use of cascara twenty-four hours before the administration of the drug.

(2) A fat-free meal is taken by the patient about 6 p.m., and the drug is taken one-half to one hour after the meal. It may be suspended in water as

that a practical means of anastomosis was available. Improvements in vascular suturing methods, however, have led these writers to abandon the use of the tube and to make their anastomoses by suturing the vein walls. The methods employed must depend upon the individual case, but the one which has generally proved most practical has been a union between the splenic and the left renal veins. As an alternative a direct union may be made between the portal vein and the inferior vena cava, and if a splenectomy has previously been performed, this may be the only method available. It is claimed that the results are better if the portal vein is divided, its upper end ligatured and the lower end implanted into the side of the vena cava, thus rendering occlusion of the anastomosis by thrombosis less likely. When performing the spleno-renal anastomosis, Blakemore and Lord in their early cases sacrificed the kidney and made an end-to-end union, but it is in many instances possible to employ an end-to-side junction, thus saving the kidney, and this is the technique which they now practise.

The technical problems of these operations are considerable; the parietal peritoneum, attachments of the spleen and retroperitoneal tissues contain masses of small vascular channels; the splenic vein may pass direct from the hilum of the spleen into the substance of the tail of the pancreas, and it may in fact have been occluded by thrombosis and not be recognizable; it may have undergone degenerative changes, making its wall unusually friable, so that it is difficult to isolate a sufficient length for making a satisfactory anastomosis; and finally, the display of the renal vessels or inferior vena cava in the depth of the wound is no easy matter.

During the postoperative period the greatest risk is thrombosis in the mesenteric vessels, and the use of anticoagulant drugs calls for careful judgment.

It is difficult to assess the results of these portal systemic venous shunts because occasionally ascites due to cirrhosis of the liver disappears spontaneously, whilst the intervals between hæmorrhages are very variable, but Blakemore's earliest patients operated on in 1945 have remained symptom free, and of our own series, the first patient with Banti's syndrome operated on in May, 1947, has had no further hæmorrhage, and a patient with cirrhosis of the liver operated on in September, 1947, has had no return of her ascites.

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FIG. 3a.—Normally functioning gall-bladder with opaque calculi.



FIG. 3b.—Same patient. Film two hours after fat meal showing the degree of contraction which has taken place.



FIG. 4.—Normally functioning gall-bladder containing non-opaque calculi.



FIG. 1.—Gall-bladder, full of calculi, adherent to hepatic flexure in which it produced inflammatory changes.

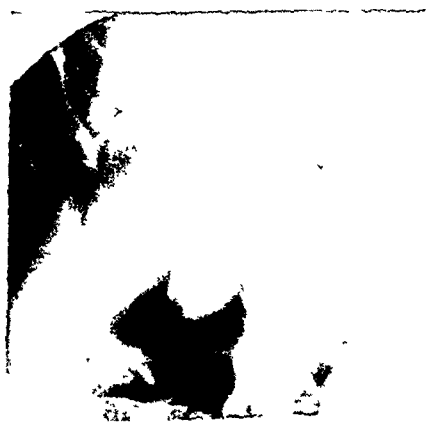


FIG. 2a.—Normal gall-bladder: patient prone.



FIG. 2b.—Normal gall-bladder same patient erect.

powder or granules, or the tablets may be swallowed unbroken and followed by a glass of water. A further glass of water is taken to wash away any remaining particles of powder or granules which might produce a burning or tingling sensation in the mouth. Nothing further should be taken by the patient before the X-ray examination except cream-free tea or coffee.

(3) A film of the gall-bladder area is taken fourteen hours after the dye has been taken, i.e., at 9 a.m. This film should be inspected immediately in order to decide if a fatty meal is necessary or other views required.

(4) The fatty meal is necessary when translucent areas are seen over the gall-bladder shadow, and the site of these, whether within or without the cholecystic outline, must be proved. Constriction of the outline should gather the translucent areas more closely together if they are calculi, and so use for this meal often arises. It may also be necessary to administer 0.5 ml. of pitressin intramuscularly, to produce peristalsis in the colon and so pass to a more distal part of the bowel any gas shadows in the hepatic flexure which may overlap the gall-bladder outline.

(5) Further expedients are the use of films taken with the patient in the upright posture (Brailsford, 1937; Ettinger, 1936) or in the right lateral recumbent posture (Kirklin, 1935).

Certain writers contend that a full and accurate diagnosis may be given from a single examination, but this has not been my experience. I have found it necessary, when a poor shadow or non-filling is observed, to repeat the examination after a further dose of dye the same evening, as sometimes a satisfactory shadow is seen from which a positive or negative diagnosis may be made at examination the following morning. The reason for this is probably slow or inadequate absorption of the dye from the small intestine, which in certain cases requires more dye or longer time to permit of adequate absorption. This fact is important, as the radiologist's constant endeavour is to have as few as possible of these doubtful cases.

Radiological technique is all-important in cholecystography, and the use of a high-speed Potter-Bucky diaphragm, rotating anode tube, short exposure, small cone, and complete abolition of movement are essential to the production of a high-class cholecystogram.

If a fatty meal is given, a further film is made fifteen minutes after completion of the meal, and at this time the cystic and common bile ducts may often be demonstrated. If further contraction of the gall-bladder is desired, this can usually be seen on a film taken two hours after the fatty meal. The chief use of these films is to enable differentiation to be made between intrinsic and extrinsic biliary shadows. The response to fats seems to be rather slower with pheniodol than with the original drug used, although it is difficult to understand why this should be so.

Pheniodol is eliminated by the kidneys after re-absorption from the bowel, and about 75 per cent. is excreted within three days. The only contra-indication to its use is severe renal insufficiency.



R.

FIG. 5.—Non-functioning contracted gall-bladder containing opaque calculi, and also a calculus in the cystic duct.

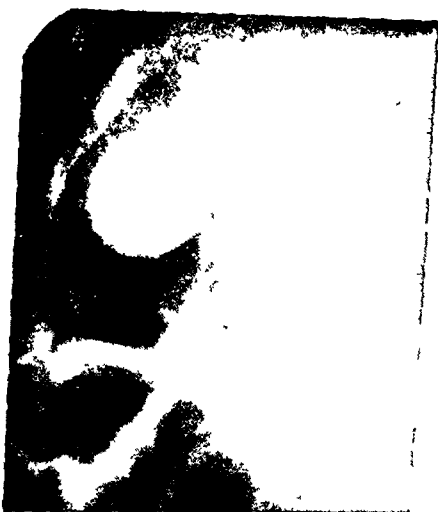


FIG. 6a.—Patient prone, preliminary film showing "milk of lime", and a calculus in the cystic duct

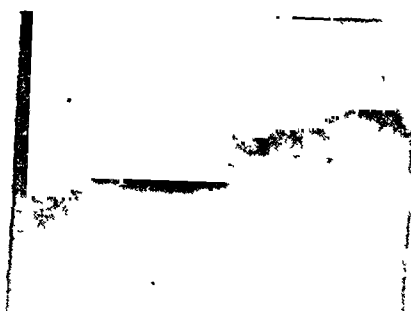


FIG. 6b.—Postero-anterior film with patient in left lateral position. A fluid level between the "milk of lime" and the inspissated bile.

essential to the demonstration of immobility of the translucent shadow within the cholecystic outline in both types of tumour.

(c) Carcinoma of the gall-bladder can be, and has been, diagnosed on rare occasions; careful study of the outline of the shadow may reveal irregularity of outline before the onset of jaundice. Case (1948) has found such a tumour; gall-bladder function was still good in this patient.

FALLACIES IN INTERPRETATION

(a) Renal calculi, calcified glands, cysts and calcified aneurysms have all been mistakenly diagnosed as biliary calculi, and it is essential in any doubtful case to carry out full investigation to confirm the presence of doubtful shadows within the gall-bladder.

(b) Gas shadows in the bowel are the most troublesome met with in radiology. Radiography in several positions and the use of pitressin usually enable a correct diagnosis to be made.

Fine non-opaque calculi may easily be overlooked unless meticulous examination is carried out. It is in this group of cases that most mistakes are made.

CONCLUSION

It has been stated that cholecystography is 95 per cent. accurate and a normal shadow means no disease in 90 per cent. of cases. Non-filling of the gall-bladder means disease in 95 to 98 per cent. of patients, but to attain this high accuracy each patient's examination must be meticulously supervised.

Cholecystography is a highly accurate method of assessing the condition and function of the gall-bladder. It is much more reliable than any other method at present available. It is also of great value in the localization and differentiation of tumours and calcified shadows which occur in the right upper abdomen, many of which may prove eventually to be extra-biliary.

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RADIOGRAPHIC FINDINGS

(1) *Normal function*.—The gall-bladder fills well and presents a smooth even outline of uniform density, which remains, although smaller in size, if a fatty meal has been given. Films in different positions may be necessary to eliminate overlying gas shadows. The shape of the gall-bladder is of little consequence as few of the variations have any pathological significance, unless persistent deformity and fixation can be demonstrated (fig. 2a, b).

(2) *Normal function with opaque calculi*.—These calculi should be demonstrated on the preliminary film, but may be equivocal in appearance and necessitate the use of cholecystography to confirm their presence within the gall-bladder which shows normal function. The calculi are usually of bilirubin-calcium, vary in size, and may be small, numerous and faceted (fig. 3a, b).

(3) *Normal function with non-opaque calculi*.—These calculi are pure cholesterol stones. This is the type of case in which very careful examination may be essential to confirm the presence of these translucent areas within the gall-bladder. Poor filling of the gall-bladder makes accurate diagnosis exceedingly difficult and therefore a second dose may be most valuable in obtaining a better shadow. If a film is taken in the erect or lateral recumbent posture, these stones may "float" in the bile and form a translucent band across the gall-bladder (fig. 4).

(4) *Non-functioning gall-bladder with opaque calculi*.—The stones are demonstrated on the preliminary film, but when the shape and texture are equivocal the diagnosis has to be made from their appearance and position, as the gall-bladder fails to fill with the dye (fig. 1 and 5).

(5) *Calcified gall-bladder*.—The diagnosis is made from the preliminary film, as there is usually complete failure of gall-bladder function.

(6) In rare instances, the gall-bladder may be found *uniformly opaque* in the preliminary film when it contains "milk of lime", which is almost pure calcium carbonate in inspissated bile. Sometimes bilirubin-calcium calculi are present and may be impacted in the cystic duct to produce the chronic obstruction which is necessary to the occurrence of "milk of lime" (fig. 6a, b).

(7) *Non-functioning gall-bladder*.—Two attempts to outline the gall-bladder should be made before accepting the diagnosis of a functionless gall-bladder; this may, and often does, contain non-opaque calculi.

(8) *Functioning gall-bladder with tumour*.—Two types of tumour are occasionally demonstrated (Kirklin, 1935).

(a) A papilloma usually occurs a short distance above the fundus and is best demonstrated after a fatty meal. It occurs in about 0.3 per cent. of gall-bladder examinations.

(b) Adenoma: This tumour occurs in about 2 per cent. of examinations, and is almost always at the fundus. As in the case of a papilloma, it is usually seen only after a fatty meal. The use of more than one position is

PRE-FRONTAL LEUCOTOMY

colouring that was changed. Among the early cases there were no deaths nor major complications, and intellectual impairment was derived. It is true that the published data were meagre and in some respects seem unreliable, but the results were sufficiently encouraging.

Despite widespread criticism and even hostility, the matter was persistently pursued by the American pioneers, Freeman and Watts, who crystallized six years' experience in a brilliant and exuberant monograph called "Psychosurgery" published in 1942. Meanwhile the operation has been taken up in many other countries, especially the British Isles, where it has so increased in favour that it is probable at the present day that more brains have been leucotomized here "per head of population" than anywhere else in the world. Although the *modus operandi* is far from clear, although the outcome is sometimes unexpected and the postoperative course difficult to predict, the results of this operation are quite good enough to justify continued use.

TECHNIQUE

The most popular technique so far evolved, and the standard one at present so far as it is the most generally used, is as follows:—

A trephine hole is made in both sides of the skull, at a point 5 to 6 cm. above the zygoma in a plane 3 cm. behind the lateral margin of the orbit. Through this blunt instrument is introduced into the hemisphere on each side successively, is pivoted up and down so that the white matter forming the centrum ovale is to greater or lesser extent divided. The instrument must be blunt to minimize hæmorrhage, but many different kinds have been used, notably a brain needle, a septum elevator, a paper-knife, and various special devices, some with rotating blades. The operative site, which corresponds to the plane of the coronal suture, lies just in front of the tip of the anterior horn of the lateral ventricle, is the site at which through trial and error has so far yielded the best results. Incisions more than about a centimetre anterior to this plane tend to be inadequate in their effects, incisions more than about half a centimetre posterior to it are liable to be fatal, so that if death is not rapid, the patient develops an intense lethargy, with trophic changes leading to bedsores and blisters, and a gradual decline to death from inanition. With regard to the extent of the incision, it is of course impossible, since the technique is a blind one, to be sure just how much of the white matter has been divided and in what precise plane. Post-mortem studies show that there is considerable variation between what the surgeon hopes to cut and what is in fact cut.

The blind approach, the variation in the size, topography and content of individual skulls, and the undeterminable amount both of intentional and accidental damage probably account for much of the variation in clinical results. These might seem arguments for a more open operation, but there are weighty arguments against it. Although there was doubt at the point at first, correlation of the clinical findings with the patient's condition by a group of pathologists (especially on material obtained from cases which had survived the operation, to die later of unrelated causes) does now suggest that the more complete the division of the central fibres, the more obvious is the operative result. The object of the present standard technique is therefore to sever the fibres of the centrum ovale at the operative site, and

PRE-FRONTAL LEUCOTOMY

A SHORT ACCOUNT OF A SURGICAL SURPRISE

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BIZARRE illnesses may require bizarre treatment, and in psychiatry they often get it. There is often a stubbornness and an antisocial quality about such conditions which evoke aggressive reactions from the frustrated therapist. Hence from earliest times there have been forms of psychiatric treatment characterized by an energetic violence. Almost every day of the week hundreds of psychotic patients are dispatched by huge doses of insulin into states of deep coma with prodigious diaphoresis. A fallacious chain of reasoning has also led to the throwing of patients into convulsions by massive electric currents. No less extraordinary than the treatments themselves is the fact that they confer much benefit. Of no treatment is this more true than of that which is the most bizarre of all, and so far the least exploited, by which, through trephine holes in the skull, the brains of the patients are stirred up by a blunt instrument.

This operation (known as pre-frontal leucotomy; in the United States as lobotomy), originally devised by Egas Moniz, professor of neurology at the University of Lisbon, was based on the notion that by disorganizing the neural pathways it should be possible to disorganize the psychic processes which it was their function to mediate; and therefore in cases in which there were delusions of a fixed and incorrigible kind it might be possible to dislodge them by destroying the anatomical arrangements subserving their formation. This was a crude concept, involving naïve notions as to the origins of "mental" illness, but there is some truth in it, if not quite in the way that Moniz himself believed. The idea of the operation was encouraged by the observations of physiologists at that time, notably Fulton and Jacobsen, on the behaviour of chimpanzees after removal of the frontal lobes. These animals were found to be calmer and less temperamental, at the cost of apparently small intellectual deficit. That such extensive interference could produce so little adverse change augured hopefully for the same in humans.

Moniz initiated the work in 1935. The operations were done by his surgical colleagues, at first by causing very limited destruction of nerve fibres by injection of drops of alcohol into the frontal lobes, and later by cutting out of them small spheres of white matter with a specially devised wire loop. The results were not quite what was expected. Generally speaking, the delusions and hallucinations, which it was thought might be interrupted, were still persistent; but, as with the chimpanzees, the agitation and distress were abated, so that the delusions and hallucinations were much less upsetting to the patient. On the whole therefore it was the emotional

CLINICAL APPLICATIONS

if something similar to the process described does happen we have in already noted in Jacobsen's chimpanzees and Moniz's early cases. Indeed, since then one of the points on which there has been unanimity is that the operation relieves what nearly all writers refer to as "tension". This, as opposed to relaxation, implies activity and expenditure of energy. It is experienced subjectively as an inability to relax; the accompanying emotion varies between feeling ill at ease and frankly anxious. In behaviour it is expressed by restlessness, often punctuated by efforts to gain relief in the form of irritable outbursts, impulsive acts, violence, crying or undue clinging. Physiological manifestations tend to be anorexia, loss of weight, insomnia, sometimes with diarrhoea and frequency of micturition. Physical manifestations tend to be tachycardia, tautness of muscles with increased reflexes, tremors and sweating. Not all of these are constant, and they depend upon the chronicity of the condition. The presence of tension has become a *sine qua non* in the decision whether to operate or not.

Pre-frontal leucotomy is thus not a specific treatment, but a symptomatic one, of the suitability for which a mere diagnostic label is no criterion. This operation is being used in cases of schizophrenia of all types, in both manic and depressive phases of manic-depressive psychosis, in any kind of depressive state involving agitation, in cases of psychopathic behaviour with high emotional colouring, in the behaviour disorders of postencephalitic and epileptic states, in obsessional neuroses, and in cases of intractable pain. As with other forms of symptomatic treatment, the underlying condition is not necessarily changed; the alteration is more often in the patient's attitude towards it. In cases of *intractable pain*, for example, the patient may change from being hopelessly demoralized, self-centred, demanding of and dominated by drugs, to being extraordinarily tolerant of his symptoms, ceasing to make spontaneous complaints and to ask for drugs, sleeping without them, enlarging his interests and even perhaps resuming his former life. Yet, the underlying lesion has been untouched by the operation, and the patient, when asked, will say that the pain is just the same. *Obsessional patients*, likewise, may retain their obsessions to a large extent, but unless the symptoms are very deeply entrenched they will be less dominated and distressed by them. In cases of *psychopathic behaviour*, too, the sort of emotional displays great enough to bring the patient to operation (e.g., as in a recently reported case, the repeated breaking of plate glass windows, followed by rubbing the elbows on the jagged points of glass, with severance of the underlying structures down to the bone) are likely postoperatively to be less florid, but it would be optimistic to hope that all psychopathic traits would be thus removed.

Again, in some *depressive conditions*, particularly if they are of long standing, the patient may remain depressed postoperatively, with low spirits, lack of interest and feeling, with poor capacity for enjoyment and indifference towards the future. This, paradoxically enough, may coexist with a super-

ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS

These researches on post-mortem material have not only made contributions to anatomical knowledge, but have provided grounds for further speculation as to the *modus operandi* of leucotomy.

The great majority of the fibres cut belong to the thalamo-frontal radiation, i.e., those fibres which stream from the thalamus to the frontal poles, the greater part of which originate from the dorsal medial nucleus of the thalamus. This was the connexion which, twenty years ago, Elliot Smith so startlingly claimed to be the most special endowment of man. It would certainly appear to have a peculiar, if unexplained, importance. The rest of the anatomical findings must be over-simplified by saying that they indicate that the pre-frontal cortex and the anterior cingular cortex (lying on the medial surface of the hemisphere adjacent to the corpus callosum) both play an important rôle, together with the thalamus and hypothalamus, in an intimately connected and coordinated system. Now, comparative anatomists have for some time realized that the temporo-parietal, rather than the frontal, areas, are the main determinants of man's intellectual superiority. From mere consideration of the arrangements they have long been doubtful of the alleged major importance of the frontal lobes in intellectual function, and have tended to regard them more as receptor areas for afferent stimuli from the hypothalamus, transmitted *via* the thalamus.

As to the nature of such stimuli, the physiologists have been accumulating evidence over the years. To summarize this must also be to over-simplify it.

The thalamus is the great reception centre for afferent stimuli, and it seems to have the function both of integrating these into percepts and of giving them some emotional investment, so that by this agency they enter consciousness and become subjective experience. It appears from animal experiment that there must be some thalamic awareness of this sort, if a primitive one, since a decorticate cat, for example, will show anger at a barking dog. The thalamic experiences are no doubt elaborated, enriched and prolonged by their distribution to the cortex, in course of which they presumably arouse further associations with their own accompanying emotions, so that by this amplification of the thalamic stimuli by cortical action the conscious life finds fuller expression.

The hypothalamus, on the other hand, plays a crucial rôle in effecting the bodily changes with which we react to our environment. Thus, the pulse and respiration rates, the blood pressure, the tone of the hollow viscera, the temperature, hydration, level of blood sugar, and the general degree of waketulness of the person, are all dependent upon hypothalamic influences. And, in so far as these are reflections of the emotional state, it may be said that the hypothalamus mediates the somatic expression of emotion and controls the tension at which we live.

It would therefore seem that the hypothalamus provides by its influences the milieu for the conscious experience of those emotions mediated by thalamic activity, which are enabled to reach a more mature expression by cortical processes. The cortex, thalamus and hypothalamus function inter-dependently, forming units in a system the component parts of which reciprocally influence each other.

Anatomical and physiological considerations thus indicate that pre-frontal leucotomy as at present performed exerts its effects mainly through the comparative isolation, due to cutting of the connexions, of the pre-frontal cortex on one side of the incision from the thalamus and hypothalamus on the other. And the resultant changes would presumably be noticeable mainly in the emotional sphere.

alarming complications as hemiplegia, or intracranial infections, which were not infrequent in the early American cases, are now only very rarely seen.

Epilepsy is said to occur, however, in about 3 per cent. of cases. In a series of 300 cases recently investigated by me, 14 had developed epilepsy within two years of operation, but the attacks were controlled by medication in 6 out of the 8 patients who took it. When epilepsy exists before the operation the incidence of attacks does not appear to be affected. In the same very varied series of cases, the relapse rate among the recovered patients, in the sense of having been discharged home free from their preoperative syndromes, was 6.5 per cent. between one and two years after operation.

At the *physiological level*, appetite and weight are almost always increased, although not necessarily in parallel; both tend to settle within normal limits within twelve months, but a few patients, nearly always women, continue to get steadily fatter. Sleep tends at first to be peculiarly heavy and dreamless. Menstruation, if disordered by the illness, usually returns to normal and dysmenorrhœa is rarely complained of. These changes are probably due to abolition of cortical influences on the hypothalamus, and also through that on the pituitary body. Urinary incontinence often, and fæcal incontinence sometimes, follow operation, but the latter appears always to be transient, and the former nearly always so, although mild degrees of urgency of micturition may be lasting sequelæ. This is probably due to interference with connexions between the pre-frontal area and the paracentral lobule.

At the *psychic level*, there is characteristically a marked postoperative lethargy, sometimes with disorientation and confusion and some admixture of restless excitement. Within a few weeks the postoperative personality begins to emerge, and here it seems easiest to consider the changes under three headings: those in activity, those in affect (i.e. emotion), and those in restraint.

In *activity* there is a shift from restlessness towards inertia. There is difficulty in getting up in the morning; there is a tendency to sit about rather than to do things during the day, and to go to bed earlier at night. Paradoxically, there is occasionally an excessive restlessness amounting to over-activity. This is difficult to explain but might be due to accidental damage to area 13 or its projections on the orbital surface of the hemisphere. Even when overactivity occurs, it is my experience that it is punctuated by frequent rests, undue fatigability, and retirement to bed by 7.30 or 8 p.m.

This tendency to inertia is reflected in the *affective sphere* by an increase in placidity and by being emotionally less "keyed up". "It isn't worth worrying", the patients often say, and when worry would have implied activity and effort, now the absence of worry implies inertia and acceptance. The two combine to make for an absence of what may be called striving. In this absence of striving the satisfactions of life become simpler, and the patient follows a naïve pattern of avoiding discomfort in favour of simple pleasures. There is thus a tendency to keep the best armchair, and when a

ficial appearance of euphoria characterized by giggling of an automatic kind, making sharp sallies, frivolous conversation and irresponsible levity, which may delude the incautious observer that depression is no longer present. In such cases it would seem that the agitation, the chronic worrying with anxious doubts and wonderings, the fearful apprehensions about the future, all removed by the operation, were but the elaborate emotional reactions of the sufferer to that essential nucleus of depression which still remains. This finding, considered in conjunction with the poor postoperative results in the contrasting condition of chronic mania, the rather frequent tendency to relapse in periodic mania, and the considerable clinical evidence available that manic reactions are associated with hypothalamic lesions, I consider as very suggestive that both manic and depressive phases of manic-depressive psychosis may arise from dysfunction of certain cell groups in the hypothalamic nuclei. Thus, to operate above the level of the lesion is perhaps but to limit, by reducing the number of available nervous pathways, the emotional repercussions (whether of manic excitement or of depressive agitation) with which the patient reacts to the basic disturbance itself, and which preoperatively were elaborated through the very thalamo-cortical system which the operation of leucotomy destroys.

In the *schizophrenic group of illnesses* also, there is a tendency for the underlying schizophrenic manifestations to remain, although the agitated and impulsive behaviour, the excitements and their antisocial consequences may fall into abeyance. Thus, it is in the more florid forms with marked emotional disturbances that the best results occur. Yet, strangely enough, there are sometimes actual "cures", occasionally even in the unemotional hebephrenic types of insidious onset. This is very odd, but some reflection may make it seem, perhaps, less inexplicable. The thalamus is an integrating organ. The essence of schizophrenia, as its name implies, is disintegration. The thalamus, it appears, integrates perceptions, emotions and patterns of behaviour. Schizophrenia is especially characterized by disturbances of perception, emotional incongruity and disordered behaviour. There are other things to be said, but these are the most obviously suggestive, and when it is considered that some schizophrenic cases are cured by an operation which seems to exert its primary influence on the thalamus, they become more so. It might be too much to say that the clamant manifestations of schizophrenia are also manifestations of disordered thalamic activity, but such a concept would none the less seem to offer a rational point on which to focus considerations of this irrational disease.

POSTOPERATIVE CHANGES

These are so variable and so individual as to defy accurate description in general terms. The mortality is about 3 per cent.

The most frequent operative complication is *hæmorrhage*. Patients with blood pressures as high as 220/160 mm. Hg have survived operation, but hyperpietic women seem to tolerate it better than hyperpietic men. Such

for effort. But this is not my view: I believe that when the tests show no impairment, it is because they are not sufficiently refined.

SUMMING-UP

When all this has been said, we are left with the difficulty of conveying the extent to which such changes actually occur. There is no constancy. Not only is there great variation from case to case, but there is great variation in the same case at different times. Awkward, aggressive and unpleasant patients may behave admirably before strangers, or before relatives who do not arouse old antagonisms; careless and dilatory patients may in some circumstances display great punctilio; grossly inert patients may become animated at parties. Then again the postoperative state, which may always be coloured by some residua of illness, is not static, but is continually changing even if slowly, and changing over months and even years, on the whole for the better. This is presumably because the dynamic functioning of the nervous system enables the functions of one part to be taken over, to some extent, by another. Whatever the cause, there is usually a marked increase in activity and animation within six and twelve months after operation, and after two years many patients are normally spontaneous.

If the postoperative picture seems a gloomy one, it must be borne in mind that the great majority of patients operated upon are almost hopeless chronic invalids, and that many, after operation, are able to support themselves; that those who are difficult to live with were for the most part so before, and that sometimes there are virtually no personality changes at all. In my experience between 60 to 75 per cent. of discharged patients live with their relatives on harmonious terms and are a pleasure rather than any source of nuisance to the family. When they are not, the patients themselves seldom have any regrets, and that too must be respected. The post-operative state is compatible, to my knowledge, with resumption of work as a University professor, as a doctor, as a trained nurse, in various skilled occupations, and with being accepted for the Services. This is not to say that the patient is what once he was, but it indicates a level of function that, though reduced, may be far from useless.

It must be a general principle that this irreversible procedure, which is so little understood and which may be fraught with grave results, is undertaken not lightly, but as a last resort. All other means of appropriate treatment should first be tried. If the patient is able to earn his own living, his symptoms must constitute the heaviest burden before the decision to operate is made. On the other hand, when the patient is incapacitated, is deteriorating, and other treatments have failed leaving a bad prognosis, too great hesitation need not be felt. Strange and irrational though this procedure seems, it is remarkable how few patients are rendered worse (and how rarely are they themselves aware of it). In assessing the value of this operation, the strongly adverse criticisms sometimes raised have nearly always arisen from an inadequate appreciation of the deplorable preoperative state.

dish of five plover's eggs is served for two people, the leucotomized patient, like Cornus Bassington, will probably take three. Procrastination is noticeable, but chiefly for those things the patient does not wish to do. Likewise, in the avoidance of effort, obligations may be neglected, the feelings of others disregarded, kindnesses and special attentions taken for granted. The range of interest becomes correspondingly less: problems are dismissed, world affairs recede in favour of immediate issues; gossip and trivialities take the place of abstract speculation. All this is accepted by the patient, usually with little insight into any change, for the failure to worry, whilst beneficial in enabling him to lose his fears and fancies, implies a failure of self-criticism also. Thus, in the absence of worry the patient looks outward rather than inward, but yet may be more egocentric, if in a different way.

These developments which arise basically from the lowered tensions, may be facilitated by the *lessened restraint*. Thus, the voracious appetite may remain unchecked; sexual demands may become excessive but, probably on account of the lowered drive, this is by no means common. There may be over-indulgence in alcohol if available, but surprisingly little distress if it is not. There may be an increased candour, with free expression of annoyance, especially when fatigue is felt towards the end of the day. When there are bursts of rage, however, they are seldom intensely felt, and within a few minutes the patient has forgotten them. There may be some extravagance, but it is seldom marked. The new-found freedom, arising from relief of distressing symptoms, facilitated by unrestraint, and enhanced by lack of self-criticism, enables once diffident people to lose self-consciousness and gain *self-confidence*, sometimes to the point of being patronizing. The combination of these leads to some complacency, with lack of insight, which, especially in face of serious situations calling for effort and concern, may amount to fatuousness and irresponsibility.

All these changes, in my opinion, take place within the framework of the previous personality. An aggressive, jealous person, given to sarcasm, will show such traits postoperatively in exaggerated form, when his restraint is less. But a sweet-tempered woman will not become a termagant, and those people basically well-disposed, whose irritability and tiresomeness have been essentially products of distress and fear, will be restored to something nearer their normal selves. These are the patients who, after operation, are sometimes declared to be better than they have ever been.

It remains to consider the *intellectual changes*. It is commonly said that this operation does not impair intelligence, but it is most difficult for the clinician to accept this view. The thinking is more factual with less tendency to speculation; it is in concrete rather than in abstract terms. Concepts are more difficult to form; piquancy and imaginative flights are lost. There is less spontaneity and less power of association. There is difficulty in alternating the attention, in keeping several items in mind at once, and in learning things that are new. It may be alleged that all this is due to a change of attitude, second only to the lowered tensions and the diminished capacity

symptoms of disturbance in motility. The one who had these moderate side-effects complained of some degree of fullness after eating a meal of average size, occasional belching of foul-smelling gas, and also vomiting about once a week. These side-effects did not handicap the patient in any way. The one who had marked effects complained of bloating after the evening meal and vomiting two or three times a week for relief. The one who had the moderate side-effects was considered to have obtained a fair result,* and the one who had marked side-effects was considered to have a good result* from vagotomy.

DUODENAL ULCERS

Eighteen of the 29 patients were operated on for duodenal ulcer. Only 5 of these 18 underwent vagotomy without some other surgical procedure. Two of these 5 patients had excellent results, 1 had a good result (insulin test, negative) and 2 had fair results. The 2 who had fair results* obtained partial relief of their abdominal distress but continued to have some symptoms suggestive of ulcer. Results of the insulin test were negative in 1 case and it was not carried out in the other.

In four cases excision of the duodenal ulcers with pyloroplasty was performed with excellent results and reduction in gastric acidity. Similarly satisfactory results, as might be expected, were obtained in 6 of the cases of duodenal ulcer in which posterior gastro-enterostomy was associated with vagotomy. In 2 cases the gastro-enterostomy was made anterior to the colon: 1 patient had an excellent result, whilst the other had a fair result with approximately 75 per cent. relief of pain after twenty-seven months. This patient had a negative finding on insulin test.† In 1 case vagotomy and resection of two-thirds of the stomach were carried out with excellent results.

GASTRIC ULCERS

Five of the 29 patients had gastric ulcers. All 5 had complete relief of pain and negative results were obtained from insulin tests. Four had vagotomy alone. The fifth underwent vagotomy and excision of the small gastric ulcer. This patient had extensive associated gastritis. Although he has had complete relief of pain and has gained approximately 20 pounds (9.1 kg.) in weight in the several months since operation, gastroscopic and radiological examinations revealed the same degree of gastritis as they did before vagotomy. In order to compare these good results from vagotomy, I inter-

*This is an over-all evaluation.

†In 1 case not included in the 29 a large gastro-jejunal ulcer developed after anterior gastro-enterostomy with entero-anastomosis twenty-six days later to relieve persistent gastric retention. He had a negative result from the insulin test. He has had an excellent result following removal of the gastro-jejunal ulcer and a partial gastrectomy.

THE RESULTS OF VAGOTOMY

FOLLOW-UP OF 29 PATIENTS

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SINCE the publication of my article in the symposium on "The Peptic Ulcer Problem" in *The Practitioner*, January 1949, 162, 33, I have had the opportunity of examining 29 of the patients on whom my report was based. In view of the importance of the subject, the Editors have suggested that I should publish the following summary of the findings in these patients.

Twenty-five patients have had complete relief of pain after an average follow-up time of eighteen months. In 24 of these patients, results of insulin tests were negative two and a half weeks after operation and have remained negative. In the twenty-fifth case the insulin test was positive after surgery; eighteen months later it was negative. In 4 cases either the ulcer failed to heal or there was recurrence after operation. At the time of re-examination, however, only one of these patients had a negative reaction to the insulin test. Two had positive reactions and on one the test was not done.

GASTRIC MOTILITY

In 24 of the 29 cases in which re-examination has been performed at the clinic there was a loss of gastric motility and tone two and a half weeks after operation as determined by radiological examination. In 20 of these 24 cases motility had apparently returned to normal in approximately nine months, because the feeling of fullness had disappeared and belching and nausea had ceased. When these patients returned to the clinic later, radiological examinations verified the return of gastric motility to normal. In 22 of these 24 cases insulin tests gave negative results, in 1 case a positive result, and in 1 the test was not carried out.

In 4 of the 24 patients, gastric tone failed to return to normal after an average of thirteen months. In 2 of these 4 there have been disturbing symptoms in which even after meals of moderate size they experienced considerable epigastric fullness with vomiting on the average of once a week. In addition, they frequently belched foul-smelling gas.

In 4 of the 5 cases in which no loss of gastric motility or tone was found on radiological examination immediately after operation, results of the insulin tests were negative and in the fifth case they were positive. These cases are rather interesting as a variable response to vagotomy occurred in cases in which the insulin test was negative.

At an average of fourteen months after operation 27 of these 29 patients reported that they had no troublesome symptoms indicative of disturbances in gastric motility. Two had what were considered to be moderate or marked

symptoms of disturbance in motility. The one who had these moderate side-effects complained of some degree of fullness after eating a meal of average size, occasional belching of foul-smelling gas, and also vomiting about once a week. These side-effects did not handicap the patient in any way. The one who had marked effects complained of bloating after the evening meal and vomiting two or three times a week for relief. The one who had the moderate side-effects was considered to have obtained a fair result,* and the one who had marked side-effects was considered to have a good result* from vagotomy.

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Five of the 29 patients had gastric ulcers. All 5 had complete relief of pain and negative results were obtained from insulin tests. Four had vagotomy alone. The fifth underwent vagotomy and excision of the small gastric ulcer. This patient had extensive associated gastritis. Although he has had complete relief of pain and has gained approximately 20 pounds (9.1 kg.) in weight in the several months since operation, gastroscopic and radiological examinations revealed the same degree of gastritis as they did before vagotomy. In order to compare these good results from vagotomy, I inter-

*This is an over-all evaluation.

†In 1 case not included in the 29 a large gastro-jejunal ulcer developed after anterior gastro-enterostomy with entero-anastomosis twenty-six days later to relieve persistent gastric retention. He had a negative result from the insulin test. He has had an excellent result following removal of the gastro-jejunal ulcer and a partial gastrectomy.

polate an observation about 3 patients not included in the 29 reported herein:

In one, in whom vagotomy only was performed, a craterous gastric ulcer has been found on radiological examination carried out elsewhere; the patient is returning again for reconsideration. In 2 cases large benign gastric ulcers were excised because of the fear that they might be malignant; the gastric ulcers and pain recurred, and secondary partial gastrectomy was required for complete relief of symptoms.

GASTRO-JEJUNAL ULCERS

In 3 of the 29 cases a gastro-jejunal ulcer followed gastro-enterostomy. One of these patients underwent vagotomy alone with excellent results. Pain was completely relieved, no disturbances in motility were noted, and the motility of the stomach was normal on radiological examination. Gastric acidity was reduced and results of the insulin test were negative. In 1 of these 3 cases the gastro-enteric anastomosis was taken down and a Heineke-Mikulicz pyloroplasty and vagotomy were carried out. Immediately after operation the insulin test gave a positive result, gastric acids were not reduced but radiological examination of the stomach revealed normal tone. Fourteen months after vagotomy this patient had no relief from pain, results of the insulin test were still positive, and the amount of gastric acid was the same as before operation. In the third case disconnexion of the gastro-enteric anastomosis was followed by vagotomy. This patient had complete relief of symptoms twenty-four months after operation and no side-effects.

In the 2 cases in which gastro-jejunal ulcers had followed gastric resections, vagotomy alone was carried out. In both cases results were excellent nine months following surgery: relative achlorhydria, normal gastric motility and negative results on insulin tests were obtained. One patient had a gastroduodenal ulcer after gastric resection and a Billroth I anastomosis. Vagotomy alone was carried out. The result in this case was highly satisfactory. After twenty-four months the patient had a negative result from the insulin test, a relative achlorhydria and the motility of the stomach was normal.

THE EFFECT OF VAGOTOMY ON ACIDITY

Studies were carried out to determine the effects of vagotomy on the acidity in these 29 cases. In 18, free hydrochloric acid was reduced, in 10 relative achlorhydria was produced, and in 1 acidity was not reduced. The patient whose acidity was not reduced had a positive result to the insulin test fourteen months after vagotomy. One patient, having reduced acidity, had a positive result on insulin test when examined fourteen months after operation, and another patient with reduced acidity did not have an insulin test done.

I am greatly indebted to my first assistant, Dr. M. M. Fahey, who has assisted in the follow-up studies of these patients.

CURRENT THERAPEUTICS

XV.—THE VITAMIN B COMPLEX

By H. M. SINCLAIR, D.M.

Fellow and Tutor, Magdalen College, Oxford; Director, Laboratory of Human Nutrition, University of Oxford.

THE practitioner who exclaimed "Medical therapy has now become B complex" may, if indeed he had these vitamins in mind, have been inspired by the circulars of certain of the less reputable vendors of nutritional nostrums. Since an enormous number of original papers on this group of vitamins is published, he could scarcely be expected to sift for himself the vast amount of chaff from the small berry, and thereby to learn how few are the proved therapeutic uses of these extremely important nutrients. There are about a dozen vitamins included in the group. All are soluble in water but in different degree—riboflavin is only sparingly soluble; most are very distinct in their chemical constitution—although para-aminobenzoic acid forms part of the molecule of folic acid. In general, each member is as distinct chemically from another as it is from the water-soluble vitamin C, and it is historical accident that they are included together under the same letter: similar sources, such as yeast, were early used for their isolation, and they were assayed by tests on the same type of laboratory animals, usually rats. It was at first convenient to distinguish them by their stability to heat, which differentiated the labile vitamin B₁ from the more stable vitamin B₂ complex, and the latter was then subdivided by adsorption and other chemical methods. The evolution of the complex has no place in an article such as this, and it is more simple to treat each member in turn. Those to be considered are thiamine (vitamin B₁), niacin (nicotinic acid), riboflavin, pyridoxine (vitamin B₆), pantothenic acid, biotin, choline, inositol, para-aminobenzoic acid, folic acid, and vitamin B₁₂ (the newly isolated factor effective in the treatment of pernicious anæmia). No discussion will be given of laboratory methods of diagnosis which are highly specialized although very important, since clinical signs are a late manifestation of deficiency.

THIAMINE

Thiamine is also called vitamin B₁ or aneurin. In 1884, Baron Takaki eliminated beri-beri in the Japanese navy by changing the dietary; nine years later an analogous disease was produced experimentally in fowls by Eijkman by feeding them polished rice, and was cured by adding the rice polishings. The vitamin was crystallized by Jansen in 1926, and synthesized by Williams in 1936.

Thiamine hydrochloride, which is the usual form of the vitamin, is a white crystalline compound, readily soluble in water, with a smell resembling

yeast and a taste like nuts. Its structural formula is shown in fig. 1. It contains the pyrimidine and thiazole rings, and is easily broken into these

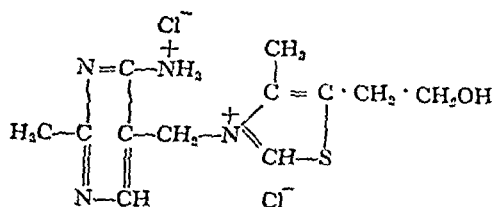


FIG. 1.—Thiamine hydrochloride.

by heat in neutral or alkaline solution, but in acid solution or in the dry state it is stable. Cooking usually destroys some of the vitamin, and more is lost in preparation of foods because of its solubility in water; further, dehydration of meats or vegetables may lead to rapid destruction. Not many foods are rich sources: those containing most thiamine include lean pork, oatmeal, high extraction flour, peas and beans. But in an ordinary dietary at the present time between one-half and two-thirds of the thiamine usually comes from bread, flour and potatoes; bacon, milk, vegetables and oatmeal contribute most of the remainder.

Dietary requirement.—The amount of thiamine required in the diet depends upon the amounts of carbohydrate and protein ingested. About 0.4 mg. of thiamine for each 1000 total calories available from the diet is a reasonable dietary allowance, a person obtaining 2500 calories from the diet would therefore need 1 mg. of thiamine. During lactation an allowance greater than that proportional to the caloric requirements is probably needed; it is desirable to add 0.2 mg. daily to the amount calculated on the basis of 0.4 mg. for each 1000 total calories.

Signs of deficiency.—It is not surprising that the requirement of thiamine should be proportional to non-fat calories, since the vitamin is known to be needed for the oxidation of carbohydrate, and fat has a sparing action upon it. Peters (1936) showed that in absence of the vitamin, carbohydrate is oxidized to pyruvate which then accumulates since it is not oxidized further, and later Lohmann showed that cocarboxylase—the coenzyme needed for the degradation of pyruvate in animal tissues and yeast—was the pyrophosphate ester of thiamine; the estimation of pyruvate in blood has been made a test for deficiency of the vitamin in man. It might therefore be supposed that those tissues that are most dependent upon carbohydrate as a source of energy would be the first to suffer in deficiency of thiamine, and such appears to be so: neurones, cardiac muscle cells (particularly the auricles) and perhaps kidney cells are affected. It is not surprising that three types of beri-beri may be distinguished clinically: dry beri-beri, affecting the nervous system; acute cardiac beri-beri with rapid heart failure; and wet beri-beri in which there is marked œdema that is not caused by cardiac failure and may be caused by increased reabsorption of water and salt in

the renal tubules. Unfortunately, however, knowledge of pure deficiency of thiamine in man is slight, and even in experimental animals the work has usually been complicated by inanition producing other deficiencies. Acute severe deficiency of thiamine in lower animals such as pigs causes bradycardia, abnormalities of the electrocardiogram, and often sudden death (Follis *et al.*, 1943); at autopsy, necrosis of the myocardium is found which may be either focal or diffuse and affects the auricles earlier than the ventricles. *Acute cardiac beri-beri* in man is the most severe of the three recognized types of beri-beri heart: it is accompanied by sudden congestive failure, præcordial distress localized to the sternum, extreme dyspnoea and a greatly dilated heart; death may be very sudden. Less severe forms are usually accompanied by oedema, mild polyneuritis, and an enlarged heart, liver and spleen. The mild form is accompanied by dyspnoea, palpitation, usually tachycardia after an initial bradycardia, and slight dilatation of the heart. In all forms there is as a rule widespread peripheral arteriolar dilatation which produces warm red limbs, a decreased circulation time and "pistol shots" heard over the peripheral arteries. The condition has been studied particularly by Aalsmeer and Wenckebach (1928) in Java, Keefer (1930) in China, and Weiss and Wilkins (1937) in the United States; the last workers claimed that cardiovascular disturbances, probably due to deficiency of thiamine, occurred about once in every 160 medical admissions to a large hospital in Boston. A good account of cardiac manifestations of beri-beri in American prisoners of war is given by Hibbs (1946). In England mild cases have occasionally been described (Konstam and Sinclair, 1940). The condition responds rapidly to administration of thiamine.

Dry beri-beri.—Although thiamine has been proved to play an important part in neurophysiology (Muralt, 1947), its relation to clinical or pathological disorders of the nervous system is not so definite as its relation to cardiac disorders. The earliest effect of deficiency of thiamine is probably anorexia, and in consequence there is a tendency for other deficiencies to arise when human volunteers or lower animals are given diets deficient in thiamine.

It appears from the work of Swank and others on pigeons that acute deficiency of thiamine may cause accumulation of pyruvate in the lower parts of the brain, and this may produce hyperæmia, oedema and hæmorrhages with lesions similar to those found in Wernicke's encephalopathy; the blindness and opisthotonos of pigeons acutely deficient in thiamine are caused by a biochemical rather than a morphological lesion since injection of thiamine cures them extremely rapidly, but Swank frequently found mild degeneration of the peripheral portions of axones of the vestibular nuclei. Chronic deficiency in his pigeons caused ataxia and paresis of the legs, with widespread degenerative changes starting in the distal parts of axones.

Sensorimotor peripheral neuritis has been produced in two human subjects by chronic deficiency of thiamine (Williams *et al.*, 1943), but unfortunately no histological observations were made upon nerves obtained by biopsy; the morphological lesion was only slowly reversible under intensive therapy with thiamine. Characteristically the neuritis of dry beri-beri is sensorimotor, starting distally in the legs, and accompanied by tenderness of the calves.

Wet beri-beri has not been produced experimentally in man by deficiency of thiamine, but there seems little doubt that it is a manifestation of such deficiency. The œdema is not cardiac in origin, and may be caused by increased capillary permeability or by increased reabsorption of water in the kidney tubules. Clinically, it is quite distinct from famine œdema (Sinclair, 1948): in this the limbs are cold and pale (although there may be acrocyanosis of hands and feet), whereas in wet beri-beri they are red and warm and the circulation time is diminished. Wet beri-beri responds rapidly to therapy with thiamine.

Obviously these three types of beri-beri—dry, wet and acute cardiac—may be present together in greater or lesser degree: it is unusual for wet beri-beri to occur without any indication of peripheral neuritis; in nine cases of “beri-beri heart” in this country before the war, all of which had low values for thiamine in the blood, neuritis was present in four (Sinclair, 1939).

Causes of deficiency.—Deficiency of the vitamin may arise in a number of ways. An unbalanced diet is unlikely to produce it in a normal person because the high extraction bread and flour now used are important sources; but patients receiving diets for gastric ulcer or fed on glucose-lemonade may become deficient. A high carbohydrate diet increases the requirement of the vitamin, and it is also increased by pregnancy or lactation, by fever and by hyperthyroidism. In certain conditions, such as gastric achlorhydria, the vitamin becomes destroyed in the gut; in others, such as diarrhœa and after entero-enterostomy or oral administration of bacteriostatic drugs, there may be decreased synthesis of the vitamin by bacteria in the gut. It is probable that deficiency of thiamine ultimately causes: most cases of gastrogenous and alcoholic polyneuritides; some but not all cases of nutritional and gestational polyneuritides, and of Wernicke’s encephalopathy; some cases diagnosed as infective and diabetic polyneuritides; no cases of diphtheritic, arsenical or lead neuritides.

There is no danger of overdosage. In definite cases of deficiency it is advisable to start with intramuscular or intravenous injection of very large amounts, such as 20 to 50 mg. daily. Later the same amount may be given orally or the injections decreased to 10 mg. or less daily. Rapid improvement may be expected in cases of early cardiac involvement or of œdema caused by deficiency of thiamine, but neuropathic manifestations may respond very slowly or not at all.

NIACIN

Nicotinic acid was synthesized eighty-two years ago, but it was not proved to be a vitamin until 1937. Since various objections were raised to the term nicotinic acid, niacin has been introduced as a synonym. It is a white crystalline substance, soluble in water and stable. It is pyridine-3-carboxylic acid (fig. 2). In the body, niacin acts as the amide in two important coenzymes, cozymase and coenzyme II, which are concerned in tissue oxidations and glycolysis.

Sources.—Foodstuffs rich in niacin include liver, meat, high extraction

flour and beer. If no beer is drunk by a British worker, he will probably get nearly a third of his daily niacin from bread and flour, and a seventh from potatoes; these foods give him about as much as he gets from a daily pint of beer. Niacin in adequate amounts prevents and cures pellagra, but pellagra is not necessarily caused by dietary deficiency of niacin. There are complicating factors in assessing the dietary requirement. First, the amino-

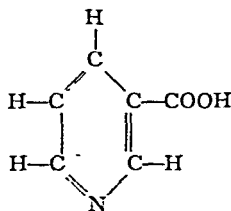


FIG. 2.—Niacin (nicotinic acid).

acid, tryptophan, can be converted into niacin in the body, and therefore pellagra is likely to arise when foodstuffs low in tryptophan, such as maize, are consumed. Secondly, certain foodstuffs such as maize contain pellagra-genic substances: 3-acetyl pyridine is such an antagonistic compound, but they are probably not important in practice. Thirdly, bacteria in the gut synthesize niacin. The dietary requirement is therefore dependent upon a number of factors, but about 4 mg. per 1000 total available calories is probably a reasonable figure in normal circumstances; this is ten times the requirement for thiamine.

Signs of deficiency.—In *pellagra* there are lesions of the skin, tongue, mouth, gut and nervous system. In the skin, there is dilatation of blood vessels in the corium giving erythema, and hyperkeratosis in the epithelium; the lesions appear particularly in areas subjected to trauma. The tongue is bald and bright red, and there may be ulcers of the buccal mucosa. Diarrhoea, which is a late manifestation, is accompanied by atrophy of the epithelium of the colon, and ulcers. The *neurological signs*, which have been described by Sydenstricker (1943), may appear before any other clinical manifestation of deficiency. Acute severe deficiency produces the abrupt onset of delirium, hallucinations or mania, which may be rapidly fatal unless niacin is given. Severe, less acute deficiency probably produces Wernicke's encephalopathy, similar to that apparently caused by deficiency of thiamine; it also is rapidly fatal unless niacin is given. Chronic and less severe deficiency produces mild psychoses similar to those produced experimentally by deficiency of thiamine: lassitude, loss of memory for recent events, apprehension and slight mental retardation; later there may be marked disorientation, confusion and sometimes mania or profound depression. In these psychotic states administration of nicotinic acid produces a dramatic response unless they are of long standing.

In the treatment of all the psychoses it is customary to give large doses initially: Sydenstricker recommends 100 mg. of niacin or 30 mg. of

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Sources.—Foodstuffs rich in niacin include liver, meat, high extraction

purple or magenta in colour because the circulation in the dilated vessels is slow. Two changes can occur in the eye: cataract and corneal vascularization. The latter, which consists of superficial capillaries passing symmetrically beyond the limbus on to the cornea, can only be examined with a slit-lamp microscope, and the unfortunate claims and confusion that have arisen regarding it cannot be discussed here. The lesion is not pathognomonic of deficiency of riboflavin, and the earlier claims that other types of keratitis (syphilitic and rosacea) respond to therapy with riboflavin have not been substantiated.

Riboflavin is almost always administered by mouth; doses of 5 to 10 mg. daily are reasonable for definite cases. Oral administration of enormous doses produces no toxic effects.

PYRIDOXINE

Pyridoxine or vitamin B₆ was synthesized in 1939, and was shown to be a derivative of pyridine (fig. 4), as is niacin. The hydrochloride is a white

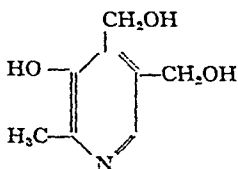


FIG. 4.—Pyridoxine.

crystalline powder with a slightly bitter taste. The richest common foodstuffs include liver, meat and high extraction flour; the daily requirement is not known but is guessed to be about the same as for thiamine. In lower animals the vitamin in the phosphorylated form acts as a coenzyme in the decarboxylation of certain amino-acids, in transamination between amino-acids and keto-acids, and in the metabolism of tryptophan, since animals deficient in the vitamin excrete a degradation product of this amino-acid—xanthurenic acid—in the urine.

In rats, *deficiency* causes an erythematous dermatitis affecting the paws, ears, nose and chin; there is hyperkeratosis and acanthosis of the epithelium, and vasodilatation with œdema in the corium. In pigs there is microcytic anæmia with high serum iron and hæmosiderosis. Lower animals also show ataxia, convulsions, and epileptiform fits resembling those seen in human epilepsy; there is demyelination of peripheral sensory neurones and later in the dorsal columns of the spinal cord.

In man, pyridoxine appears to cure certain cases of cheilosis that are not cured by riboflavin, and no other therapeutic claim has been definitely proved although encouraging results have been found in chorea (Kost, 1948). The vitamin has been used in a number of clinical conditions, such as non-postencephalitic Parkinsonism, amyotrophic lateral sclerosis, myasthenia gravis, Sydenham's chorea, arsenical neuritis, and acne vulgaris.

niacinamide every hour parenterally for ten hours during the first two days, later reducing the dose to 500 mg. daily (or 150 mg. of the amide) in five divided doses, and then 25 mg. of niacin orally thrice daily for maintenance. The amide is pleasanter to give because the acid produces marked vasodilatation in amounts of about 100 mg. or more—indeed, it has been used therapeutically in certain conditions of impaired circulation simply for its vasodilator effect. In Wernicke's syndrome or if peripheral neuritis is present, thiamine should also be given in amount equal to about one-tenth of the dose of niacin.

RIBOFLAVIN

Riboflavin, which used to be called lactoflavin and sometimes erroneously vitamin B₂, is a derivative of iso-alloxazine (fig. 3).

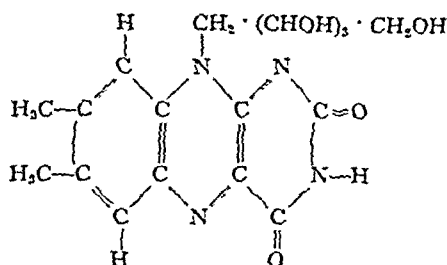


FIG. 3.—Riboflavin.

It is a yellow crystalline compound with an intense yellow-green fluorescence in aqueous solution. It is fairly stable to heat but is rapidly destroyed by light. In the body it is converted to riboflavin phosphate and then combines with proteins to form flavoproteins that are important enzymes in tissue respiration. Foodstuffs rich in riboflavin include liver, cheese, milk, eggs, high extraction bread and flour, spinach and beer. If a British worker drinks no beer, nearly half his dietary riboflavin is likely to come from bread and flour and a pint of beer daily supplies about half this amount. The daily requirement is about 0.6 mg. per 1000 total available calories; the vitamin is synthesized by bacteria in the gut.

The signs of deficiency of riboflavin are various (Sydenstricker, 1941). There is a seborrhœic dermatitis that affects particularly the hair margin of the head, the malar eminences, and the scrotum; there appears to be erythema with atrophy of the epithelium and altered activity of the sebaceous glands. Maceration and fissuring occur at mucocutaneous junctions: cheilosis is denudation of the epithelium along the line of closure of the lips and angular stomatitis occurs at the corners of the mouth, but neither of these is pathognomonic; more specific is the same type of lesion at the nares—mycterosis—and this term is reasonably extended to include the similar lesions that arise at the palpebral fissure, the external auditory meatus, the prepuce, vulva and anus. The glossitis of riboflavin deficiency consists of swelling of the filiform papillæ which lose their epithelial tufts and become

The vitamin appears to be connected in metabolism with the carboxylation of pyruvate to yield oxaloacetate. In lower animals deficiency causes erythema and hyperkeratosis.

Deficiency of biotin was produced experimentally in man by feeding 200 g. of dehydrated egg-white daily (Sydenstricker *et al.*, 1942). There resulted a fine branny desquamation of the skin, a peculiar grey pallor, lassitude and a smooth tongue. Since in this country we are unlikely to consume large quantities of raw egg-white, biotin deficiency is improbable even if bacterial synthesis in the gut is prevented.

INOSITOL

Inositol is a very stable crystalline derivative of cyclohexane, with a sweet taste and a ring structure similar to that of glucose (fig. 7). The optically

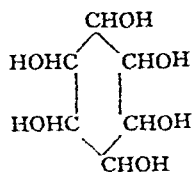


FIG. 7.—Inositol.

inactive form is the only one biologically active. It is widely distributed throughout animals and plants; in the latter it occurs free and as phytic acid—the hexaphosphoric acid of inositol—which forms insoluble compounds with calcium and magnesium and therefore tends to prevent their absorption from the gut. The action of inositol appears to be related to fat metabolism and to the action of biotin. Woolley (1940) showed that

deficiency of inositol in mice produced alopecia. Little is known regarding its rôle in human nutrition except that it occurs in certain phospholipids; it has been shown to decrease liver fat customarily found in patients with gastrointestinal carcinoma (Abels *et al.*, 1943), and has been alleged to improve the supposed action of vitamin E in the treatment of progressive muscular dystrophy (Milhorat and Bartels, 1945).

CHOLINE

Choline is a colourless, strongly alkaline viscous fluid (fig. 8), and the usual salt, choline chloride, is a hygroscopic crystalline substance with a bitter salt taste. Rich dietary sources are egg-yolk, liver and meat. It has three biological functions: it is a component of phospholipids such as lecithin;

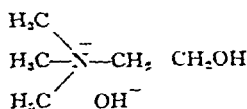


FIG. 8 —Choline.

one of its salts—acetylcholine—is important in the transmission of nervous impulses and has already been mentioned (p. 242); and thirdly, choline, like betaine and methionine, supplies labile methyl groups in the body. Deficiency of choline produces a fatty liver and hæmorrhagic

renal lesions. The dietary requirement depends upon the amount of the amino-acid, methionine, in the diet, and is probably of the order of 250 mg. daily. No definite clinical uses have yet been established, but choline chloride has been used to treat fatty liver and cirrhosis in alcoholics and in persons with poor dietary histories (Patek and Post, 1940). After failing to treat a case of Addisonian pernicious anæmia with liver therapy, Moosnick

Dramatic claims have been made, mostly better suited to drama than to therapeutics.

PANTOTHENIC ACID

As its name implies, pantothenic acid is widely distributed in nature. It was synthesized in 1940 and shown to be a derivative of β -alanine and dimethyl butyric acid (fig. 5).

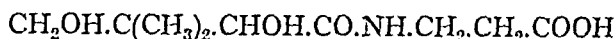


FIG. 5.—Pantothenic acid.

The free acid is a yellow oil, and the calcium salt is crystalline. The richest foodstuffs include liver, eggs, meat, cereals and milk. The human requirement is unknown, but judged by work on lower animals may be about the same as that of riboflavin. The vitamin forms part of a coenzyme necessary for certain acetylations, such as the conversion of choline into acetylcholine in nervous tissue. It is not surprising therefore that neurological manifestations should occur in lower animals: there is ataxia with chromatolysis of the dorsal root ganglion cells, and later demyelination and axis cylinder degeneration in peripheral nerves. There is also greying of the fur, alopecia in certain areas, diarrhoea, ulceration of the colon, and hæmorrhagic necrosis of the suprarenal cortex.

Pantothenic acid has no proved therapeutic use in man; but the works of Gopalan (1946) and of Peraita (1948) strongly suggest that it is effective in the "burning feet" syndrome seen in the Spanish war (Grande and Peraita, 1941) and in the last war. In the United States, backed by newspaper advertisements, large amounts have been wasted in the treatment of grey hair. Fortunately the vitamin is not toxic and up to 100 mg. of the calcium salt can be administered intravenously.

BIOTIN

Biotin is a stable compound synthesized in 1943 (fig. 6). Liver, eggs and

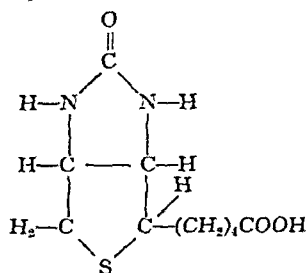


FIG. 6.—Biotin.

meat are relatively rich sources. The vitamin is synthesized by bacteria in the intestine; and its absorption therefrom is prevented if raw egg-white is eaten, because an albumin in this, avidin, combines with biotin. The human dietary requirement is probably a fraction of a milligramme daily.

CONCLUSION

There are other members of the vitamin B complex to be discovered and some have been provisionally designated. No doubt they, like the vitamins discussed here, are readily available in an ordinary dietary of natural foods. Since we are still a long way from knowing what vitamins of the B complex man needs and in what amounts, there is danger in prescribing pure synthetic vitamins: if a patient is deficient in one member of the complex he is likely to be deficient also in others, even if his clinical signs are those of a single deficiency. A pellagrin treated with niacin may immediately develop florid ariboflavinosis. It is essential therefore to adopt multiple therapy and above all to remedy the dietary defect that has led to the need for therapy. Yeast is an excellent source of all the vitamins of B complex and may easily be administered in doses of about 30 g. in warm water or milk. This amount of dried yeast provides the approximate daily requirement of the members of the vitamin B complex.

Discussion in this article has been limited to the different known members of the complex. There are certain syndromes that are probably caused by deficiency of one or more members. These include retrobulbar neuritis, spinal ataxia, spastic ataxia, and spastic paraplegia; they were studied in two of the recent wars, particularly in Madrid and the Far East, and excellent reviews have been given by Grande and Peraita (1941), Denny-Brown (1947), and Spillane (1947).

It is perhaps of interest to give a rough assessment of the human dietary requirement of members of the vitamin B complex (in micromoles daily): less than 1: vitamin B₁₂, folic acid and biotin; about 5: thiamine, riboflavin, pyridoxine and pantothenic acid; about 80: niacin; about 500: inositol; about 2000: choline. These amounts in mg. form a very approximate guide to the therapeutic dose.

SUMMARY

(1) Deficiency of *thiamine* causes: sensorimotor peripheral neuritis with marked tenderness of the calves; Wernicke's encephalopathy; cardiac failure; œdema not of cardiac origin.

(2) Deficiency of *niacin* causes: erythema and hyperkeratosis of the skin; raw red tongue; ulcers in the mouth; diarrhœa; mild or severe psychoses, including Wernicke's encephalopathy.

(3) Deficiency of *riboflavin* causes: seborrhœic dermatitis; maceration of mucocutaneous junctions; purple glossitis; cataract; keratitis.

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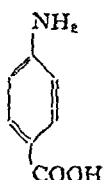


FIG. 9.—*p*-Aminobenzoic acid.

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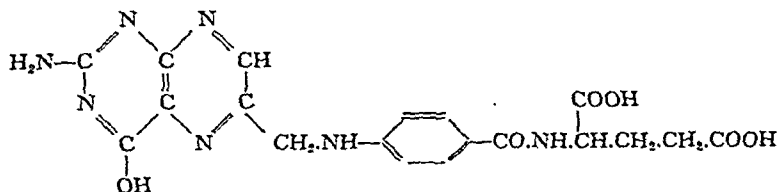


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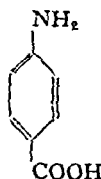


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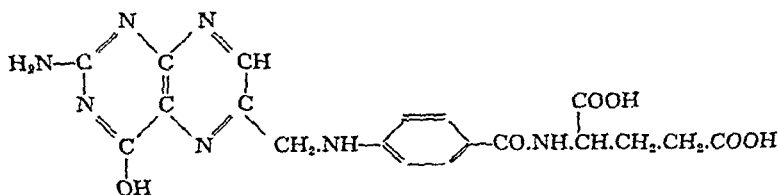


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- (7) Deficiency of *inositol* may cause fatty liver.
- (8) Deficiency of *choline* is likely to cause fatty liver if the diet is also low in protein.
- (9) Deficiency of *para-aminobenzoic acid* may cause nutritional achromotrichia. The vitamin has an important therapeutic action in rickettsial diseases.
- (10) Deficiency of *folic acid* or of *vitamin B₁₂* causes macrocytic anæmia, the latter being the liver factor effective in Addisonian pernicious anæmia.
- (11) All the above vitamins, except vitamin B₁₂, have been synthesized, and the biochemical rôles of many of them are known. They tend to be present in the same types of foodstuffs and particularly in yeast; most are synthesized by bacteria in the gut. Deficiency of only one vitamin of the B complex (except vitamin B₁₂) is unlikely.

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REVISION CORNER

THE TREATMENT OF BARBITURATE POISONING

DRUGS of the barbiturate group are the most popular hypnotics, sedatives and basal anæsthetics in general use. They are all derived from barbituric acid (malonylurea) and have been developed by chemical modification from veronal (diethylmalonyl-urea-barbitone) the father of the barbiturates, which was introduced at the end of the last century. Closely allied to them and used for similar purposes are drugs of the acetyl- and valeryl-urea type, e.g. carbromal (adalin), sedormid, planadin, bromural. The barbiturates in common use include:—

Phenobarbitone	Evipan
Prominal	Pentothal
Dial	Somnifaine
Phanodorm	Medinal
Nembutal	Veronal
Amytal	Allonal (barbiturate + amidopyrine)
Soneryl	Veramon " "
Seconal	Cibalgin " "

In some of the above preparations the sodium salt is also employed and is generally more soluble, and therefore more rapid in action and more suitable for parenteral therapy when this is required.

GENERAL ACTION OF BARBITURATES

(a) *The central nervous system.*—The main effect of the barbiturate drugs is to depress this system but their exact site of action has not been clearly defined. Some appear to act strongly on the midbrain and thalamus, whilst others have their most marked therapeutic action on the cortex (e.g. the anticonvulsant action of phenobarbitone).

(b) *The respiratory system.*—Toxic doses depress the respiratory centre and respiration becomes shallower. Cyanosis and pulmonary œdema followed by pneumonia may develop.

(c) *The bladder.*—Toxic doses may inhibit the relaxation of the sphincter muscle, rendering catheterization necessary.

(d) The differences in the duration of action of the various drugs depend upon the rate of their destruction in the body, which is mainly carried out by the liver. Barbitone (veronal) is only slowly rendered inert, about half being removed in twenty-four hours; hence the liability of cumulative poisoning. Half the dose of a short-acting drug like evipan is destroyed in about twenty minutes. Some of the drug is always excreted in the urine and some is present in the cerebrospinal fluid after administration.

Group 1.—Slow excretion (long action): includes veronal, phenobarbitone and medinal.

Group 2.—Intermediate: includes dial, amytal, nembutal, phanodorm and soneryl.

Group 3.—Rapid excretion (short action): includes evipan, pentothal, sodium amytal, seconal sodium, and other sodium derivatives.

These facts may have some bearing on the prognosis of barbiturate poisoning. Large doses of the long-acting group will tend to produce coma of long duration but of more gradual onset; whereas those of the short-action type may be expected to result in coma of rapid onset but of shorter duration. With prolonged coma the development of subsequent pneumonia is more likely to occur; whilst large doses of the short-action drugs may prove fatal before efficient treatment can be carried out. It is difficult to assess the average fatal dose as this is dependent, in many instances, upon the promptness of thorough treatment, but as a general rule it

may be stated that between five and ten times the therapeutic dose will produce serious poisoning, whilst fifteen times the dose is likely to produce a fatality if absorption is complete.

SYMPTOMS OF POISONING

Toxic symptoms, including rashes, fever, temporary mental disorders, such as delirium and hallucinations, may be due to hypersensitivity in individual patients taking normal doses. Actual poisoning most often takes place as a result of suicidal or pseudo-suicidal action. Occasionally it is said that patients having had slightly more than their accustomed dose may, in their dazed state, take further supplies while being unaware of their actions.

Depending upon how soon the patient is seen after the overdose has been taken, drowsiness, mental confusion with headache, developing into deep sleep or coma, will occur. There may be a stage of excitement with ataxia and slurred speech before loss of consciousness. The pulse tends to be increased in rate and diminished in force. The blood pressure usually falls. Respiration is shallow and the temperature subnormal. Reflexes are diminished or absent. The pupils may be fixed and are usually small but may dilate terminally. Occasionally an extensor plantar response is obtained. Pulmonary congestion and oedema are liable to develop and may be followed by fatal pneumonia, even in cases in which there has been some recovery of consciousness.

In many cases it is known that the patient has been in the habit of taking barbiturates; in others, a prescription or residual tablets may be found. The presence of barbiturates can be detected either in tablets, stomach contents, urine or the cerebrospinal fluid by relatively simple laboratory tests, which should therefore be carried out in all cases of doubt after treatment has been started.

TREATMENT

(1) *Elimination*

(a) *Gastric lavage*.—This is the most important single factor in treatment and an endeavour should be made to remove all traces of the drug from the stomach. Not less than two gallons of plain water should be used in the first instance. Lavage may be repeated two or even three times at intervals of four to six hours if necessary. Sometimes a patient may be seen before consciousness has been lost and before the necessary apparatus for lavage is available. In such instances, an emetic consisting of two tablespoonsful of salt in five ounces of water is effective, but in all but the mildest cases it should be followed by efficient gastric lavage.

(b) *Colon lavage*.—This may be of great value when carried out at intervals of twelve hours in cases in which coma is prolonged. Sometimes partially dissolved tablets, e.g. phenobarbitone, may be recovered from the washings.

(c) *Lumbar or cisternal puncture*.—In severe cases this should be carried out and repeated at intervals of twelve hours if necessary: 10 to 15 ml. of cerebrospinal fluid should be removed.

(2) *Stimulation*

In cases with cardiac or respiratory failure, nikethamide (coramine), leptazol (cardiazol), or strychnine may be given by subcutaneous injection and repeated as required. These drugs may be given by intravenous injection if necessary.

In severe respiratory failure, artificial respiration may be necessary and the use of some form of "iron lung" may be required.

Inhalations of oxygen are valuable for cyanosis but oxygen and carbon dioxide mixture has the advantage of increasing respiration and diminishing the risk of pulmonary congestion and pneumonia. In cases in which coma has been prolonged, inhalations of oxygen and CO₂ for five minutes every hour may be advisable after

consciousness has returned. Throughout the whole management of the case the patient should be propped up and turned from side to side at intervals in order to minimize the effects of pulmonary congestion. A clear airway is essential.

(3) *Antidotes*

The best available antidote to barbiturate poisoning is picrotoxin (1 ml. usually contains 3 mg.). Depending upon the severity of the case, 1 to 3 mg. should be injected intravenously at intervals of one to fifteen minutes until there is improvement in respiration, pulse and blood pressure, and the pupillary and corneal reflexes return. About this stage, twitching of the face or vomiting may occur if further doses of picrotoxin are given. The intervals between injections should therefore be increased once improvement has occurred. Pentothal sodium, evipan or a similar drug should always be available for immediate injection if picrotoxin is employed. A small dose should be given intravenously at once if convulsions occur. The use of picrotoxin should obviously be reserved for serious cases and for those which do not respond to nikethamide or leptazol. (New preparations which appear to have advantages over picrotoxin are undergoing clinical trial.)

In case of prolonged coma resulting from overdosage with a long-acting barbiturate such as phenobarbitone, it may be necessary to give as much as 200 to 300 mg. of picrotoxin, at intervals extending over four or five days. If intravenous injection is impossible, up to 10 mg. may be given intramuscularly. It will be clear therefore that no exact dosage scheme can be laid down and that each case must be judged on its merits.

Other measures which may be desirable are: (a) a course of penicillin in order to reduce the risk of pneumonia; (b) the maintenance of nutrition by the administration of 5 per cent. glucose saline, provided there is no pulmonary oedema; (c) subsequent psychotherapy in cases of attempted suicide.

W. GORDON SEARS, M.D., M.R.C.P.

THE TREATMENT OF ECLAMPSIA

ECLAMPSIA has been defined as an acute toxæmia occurring in pregnant, parturient or puerperal women, accompanied by tonic and clonic convulsions and coma, in which other diseases can be excluded. Despite a vast amount of research the cause of eclampsia is still unknown. Eclampsia can occur when a rise of blood pressure, albuminuria, or oedema, the warning toxæmic manifestations, have been present singly or in combination for only a short time; but it must be rare indeed for eclampsia to occur without any one of these ever having been present. Provided the toxæmia is recognized while it is still mild the occurrence of eclampsia can usually be avoided. Every care should therefore be taken in these cases to prevent the occurrence of fits, as the prognosis becomes infinitely worse after even a solitary fit.

PREVENTIVE MEASURES

(1) *Meticulous antenatal supervision* is the first essential. Every pregnant woman should be seen at monthly intervals until the twenty-eighth week of pregnancy, at fortnightly intervals up to the thirty-sixth week, and finally at weekly intervals until she goes into labour. The blood pressure should be taken, the urine tested for albumin, and the feet and ankles examined for oedema on each occasion. If any of the warning manifestations be present she should be seen more frequently. It will depend upon the stage of the pregnancy and upon the severity of the abnormal findings how soon a re-examination should be made. It is customary to regard 140/90 mm. Hg as the extreme upper limit for a normal blood pressure reading. In the last three months of pregnancy a moderate increase in blood pressure calls for

a further examination in at least a week's time, whilst the finding of albuminuria (other than that obviously due to a urinary infection) should call for daily examination of the urine.

(2) *When toxæmia is diagnosed* efficient treatment is the best insurance against eclampsia. For the *mild* case some restriction of the patient's activities and a daily saline laxative should be prescribed, but a normal diet should be continued, except that added salt should be avoided as this favours the development of œdema. In a *moderately severe* case (e.g. blood pressure 150/100 mm. Hg with slight œdema, or when the blood pressure is rather lower and a trace of albumin is present) complete rest in bed is the most valuable single remedy. Daily blood pressure readings and daily analysis of the urine are now required and, if œdema is more marked, a fluid intake and urine output chart should be kept. In many cases this regime will necessitate admission to hospital. If the toxæmic manifestations subside, normal life may be resumed. On the other hand, their increase may call for induction of labour. With a *very severe* case (marked headache, visual disturbances, vomiting and epigastric pain, blood pressure of approximately 180/110 mm. Hg, albuminuria, oliguria with or without œdema) rapid termination of the pregnancy by Cæsarean section may be called for to avoid eclampsia, although in one not quite so severe, heavy sedation followed by induction of labour by artificial rupture of the membranes may suffice.

MEDICAL TREATMENT

A patient who has had one fit may die, but in general the fewer the fits the better the outlook. Moreover, improvement follows the birth of the child or its death *in utero*. Treatment therefore aims at: (1) the arrest of the fits and the prevention of their recurrence; (2) procuring the birth of the child; (3) the elimination of toxins by the usual routes of excretion.

(a) *Sedatives*.—The brain is œdematous and the central nervous system hyper-irritable. To prevent unnecessary stimuli in this irritable condition the patient should be nursed in a darkened room and the nurse, in constant attendance, should wear noiseless shoes or slippers, and all other attendants should maintain quietness. Some prolonged sedation is necessary to render the central nervous system insensitive both to those external stimuli which may fall upon it accidentally, and probably also to internal stimuli from the causative factor of the disease. Some observers emphasize the beneficial results to be obtained by the use of particular sedatives—morphine, paraldehyde, avertin—but the personal attention of an experienced obstetrician familiar with the use of his chosen sedative is probably more important than the nature of the sedative actually used. Morphine is a well-tried and tested sedative. Immediately after the first fit, morphine sulphate, $\frac{1}{2}$ a grain (32 mg.), should be given by subcutaneous or intramuscular injection, followed by injections of morphine, $\frac{1}{4}$ of a grain (16 mg.), at four-hourly intervals until the fits have ceased for twenty-four hours. Not more than $1\frac{1}{2}$ to $1\frac{3}{4}$ grains (0.1 to 0.15 g.) of morphine should be given in twenty-four hours, nor should the drug be repeated if at any time the respiratory rate falls below ten per minute. In addition, chloral hydrate, 30 grains (2 g.) by mouth, or 60 grains (4 g.) per rectum, may be given between the morphine injections if the latter alone prove insufficient. This means that a sedative in some form would be given every two hours. I do not employ anaesthesia for the administration of these injections.

(b) *Eliminative measures* such as severe purgation, gastric and colonic lavage are disturbing and should be avoided. A small soap and water enema may be given to empty the lower bowel in case this route should be required for the administration of sedatives.

(c) *Urine secretion* should always be measured. The least disturbing method is to insert a self-retaining catheter into the bladder. The spigot may be removed at intervals and the urine in the bladder drained off and measured. If the urinary output is poor, intravenous fluid, six pints (3.5 litres) in twenty-four hours, should be administered by continuous drip. The first two pints (1.1 litre) can profitably be glucose, 25 per cent., and sodium sulphate, 4.285 per cent., respectively, whilst 10 per cent. glucose in water is used for the remaining four pints (2.3 litres).

(d) *Magnesium sulphate treatment* is an alternative. It is claimed to increase diuresis, diminish œdema, cause a fall in blood pressure, and control the fits.

If the fits do not cease the full dose (6 g.) of $MgSO_4$ should be given, but not more than 24 g. in twenty-four hours. Toxic symptoms which may be fatal are acute cyanosis, feeble pulse, and laboured respirations. The best antidote is 10 g. of calcium chloride as a 5 per cent. solution given intravenously. This antidote should always be available when magnesium sulphate treatment is being given.

TABLE I
PLAN OF TREATMENT

Hour	
0 ..	Morphine sulphate, $\frac{1}{2}$ to $\frac{1}{4}$ a grain (16 to 32 mg.).
0.30 ..	$MgSO_4$, 6 g. (40 ml. of 15 per cent. solution) intramuscularly.
2 ..	Morphine repeated.
5.30 ..	$MgSO_4$, 6 g. if further fits have occurred,
5.30 ..	4 g. if further fits have not occurred.
If delivery has still not taken place:—	
11.30 ..	$MgSO_4$, 4 g.
19.0 ..	$MgSO_4$, 3 g.

(e) *Fluid by mouth*.—Never should the unconscious patient be given fluid to swallow.

(f) *Position of patient*.—She should be turned gently from side to side every four hours to prevent congestion of the bases of the lungs. If the secretion of saliva or that of the respiratory mucous membranes is great it may be necessary to lower her head and to lay her in a semi-prone position to avoid the inhalation of mucus and possibly of vomit.

(g) A rubber wedge or a spoon with the handle covered with bandage should be available to insert between the teeth during a fit. A gag should be at hand, and oxygen should be readily available.

OBSTETRIC TREATMENT

The experience of obstetricians the world over is that the least possible interference the better. When the fits are under control simple rupture of the membranes may be performed if labour does not start spontaneously. Some prefer instead to perform lower uterine Cæsarean section if the fœtus is viable and likely to survive. This is an entirely different matter, however, from the employment of Cæsarean section for the treatment of a patient who is having fits. Cæsarean section done as a routine for eclampsia is bad treatment and doubles the death rate. If the patient is unconscious a watch should be kept for the onset of labour. Restlessness of sudden onset may be indicative of the imminent birth of the child.

CONCLUSION

To sum up, try to prevent eclampsia by efficient antenatal care and the prompt treatment of toxæmia. When eclampsia has supervened rely on treatment by sedatives, intravenous fluid and rational general nursing measures. For obstetric treatment be conservative and use the minimum of interference.

ANTHONY W. PURDIE, M.B., CH.B., F.R.F.P.S., M.R.C.O.G.

NOTES AND QUERIES

Postoperative Anticoagulant Therapy

QUERY.—In connexion with the heparin-dicoumarol therapy as described in *The Practitioner*, May 1948, page 413 and elsewhere, certain difficulties arise when gastrectomy cases are being considered. The average case will require a postoperative intravenous drip for some three days. Some 50 per cent. or more of the cases develop a degree of phlebitis, and in many of these cases it is impossible to be sure whether or not an element of thrombosis is present. Granted that one can cut down on the vein of the opposite leg should phlebitis develop on one side, there still remains the difficulty of deciding when anticoagulant therapy is indicated; in addition, the more intravenous therapy, the more phlebitis.

REPLY.—In the type of operation referred to, anticoagulant therapy may be indicated for one of three purposes: (1) prophylactically, to reduce the chances of thrombosis; (2) to treat thrombosis of deep veins after development; and (3) to treat thrombosis of superficial veins that have developed as a result of intravenous therapy. In my opinion it is unsafe to reduce the coagulability of the blood until the fourth day after operation and then only if it is reasonably certain that there is no infection at the site of operation. Since deep venous thrombosis probably occurs most often almost immediately after operation, "prophylactic treatment" in general must aim, not at preventing thrombosis, but at preventing the spread or break-up of any thrombosis which may have developed. When used for this purpose dicoumarol may be started on the third day (owing to its latent period) and heparin on the fourth.

Deep venous thrombosis is seldom detected before the fourth or fifth day, and then only when very carefully watched for. Since the four-day danger period has by then passed, both dicoumarol and heparin may be started as soon as the thrombosis is detected. When there is doubt as to the diagnosis of thrombosis, heparin alone may be given in the first instance. A marked improvement in the pain or tenderness over the suspected thrombosis occurring in the first twenty-four hours is strong confirmation of the correctness of the diagnosis.

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The period over which the clotting time should be kept raised ranges from about five to fourteen days, or occasionally up to twenty-one days, the period being greater the later the stage at which the thrombosis is detected, the more extensive the thrombosis, or when pulmonary embolism has already occurred. For the shortest periods heparin alone may be sufficient, otherwise both forms of therapy should be given, the heparin being discontinued as soon as the dicoumarol becomes effective. When thrombosis has only been detected at a very late stage and the danger of immediate embolism appears unlikely, it is possible sometimes to dispense with the heparin.

R. L. WATERFIELD, M.B., M.R.C.P.

What Happens to Vegetable Oils After Injection?

QUERY.—What exactly happens to arachis oil or other refined vegetable oils when administered intramuscularly as in oily penicillin injection or oily solutions of the synthetic sex hormones? Is the oil eventually split up into fatty acids and glycerol and metabolized by the body, or does it remain as an oil and eventually become fixed or lodged in some organ or tissue, more or less permanently? I know that petroleum oils are not metabolized, and remain in the tissues, but I do not know what eventually happens to vegetable oils when injected, and for that reason I have always been rather hesitant about using oily injections.

REPLY.—Despite the common use of vegetable oils as a medium for the administration of water-insoluble drugs by intramuscular injection, there has been surprisingly little investigation of the fate of these oils when lodged in muscular tissue. There is, of course, no metabolism of the oils at the site of injection. Tissue cells can oxidize fatty acids directly, but lipolysis of neutral fat in the tissues occurs only when the fat has been incorporated within the cells of adipose tissue in the fat depots.

Judging by animal experiments, oil injected intramuscularly becomes diffusely scattered within twenty-four hours in droplets, tending to accumulate along fascial sheaths but also occurring between muscle bundles. Its presence induces a moderate increase in round cells in the connective tissue. After two or three days, the oil

apparently tends to accumulate into small droplets around which there appears a layer of fibrin and a large epithelioid type of cell; at the same time, the leucocytic reaction decreases in intensity. These oil cysts range in size from microscopic to 1 or 2 mm. and have been identified in muscle up to a year after injection.

The formation of similar thin-walled oil cysts in man can only be inferred, but there is one record of aspiration of oil from an oil cyst in a patient's muscle resulting from previous injections. In patients who have died one or two months after intramuscular injection of penicillin in beeswax and peanut oil, there is usually no trace of beeswax left at the site of injection. But minute cysts with thin fibrous walls have been reported, which may well be oil cysts of the kind found in animal experiments. Different vegetable oils vary in the amount of leucocytic reaction they provoke and in the thickness of the fibrous walls of the oil cysts they form. Corn oil and sesame oil appear to produce the least reaction in the tissues. This tissue reaction provoked by intramuscular injection of oil, is, of course, different from the allergic reactions found in some patients due to hypersensitivity to some particular oil.

IAN A. ANDERSON, M.B.E., M.B., B.Sc.

Hookworm Infestation

QUERY (from Ceylon).—How long will a hookworm live in the intestine if it is not expelled by an anthelmintic? Is the anæmia of hookworm infestation due to direct loss of blood, or is it due to the toxic effect of the worm?

REPLY.—It is generally believed that a hookworm in the intestine may survive for about five years. In actual experience, however, spontaneous cure has taken place within a shorter time than this. Where ancylostomiasis is endemic, of course it may be impossible to distinguish a persisting infestation from a fresh infestation.

Several factors appear to be concerned in the production of anæmia. The worms produce an anticoagulant with toxic properties; there is loss of blood, not only that imbibed by the worms but also from damage to the mucosa, which may cause extensive extravasations of blood. It is unlikely, however, that loss of blood alone could be responsible for anæmia of the type met with, for this is not found in other intestinal conditions associated with small continued hæmorrhages. Malnutrition may also play a part, because in such states a superimposed ancylostomiasis may be the "last straw" in precipitating a macrocytic anæmia. Lastly, and especially in heavy infestations, there is considerable absorption from the intestine, believed to account for "ancylostomiasis fever". Whilst all the fore-

going are probably concerned in the causation of the anæmia, it is my belief that it is the toxic action of the worms that is most hurtful.

LIEUT.-GENERAL SIR WILLIAM MACARTHUR,
K.C.B., D.S.O., M.D., F.R.C.P.

Thumb-sucking

QUERY.—A child of three years is in the habit of thumb-sucking. The parents have tried all kinds of measures, including application of bitters, dressing the thumb, constant checking, and diverting the child's attention. The habit appears to be decreasing during the day time, but the child invariably sleeps with his thumb in his mouth.

REPLY.—Thumb-sucking is one of the most common habits developed by young children and it is considered morbid only if it persists beyond the second year. In the present case the habit is evidently clearing up at the age of three and the problem is therefore not very serious. No great harm is likely to be done if the child does sleep with his thumb in his mouth. Care should, however, be taken to see that no definite harm is being done to the teeth or mouth, or to the thumb, a rare event. At this age treatment should be indirect rather than direct, so that no terse atmosphere is created. The parents should correct any thumb-sucking during the day by engaging attention, e.g., by handing the child a toy, and no reference should be made to the habit. The parents should be reassured that the habit is not likely to injure the child's health. Removal of the parents' anxiety is perhaps the chief factor in treatment.

A. SPENCER PATERSON, M.D., F.R.C.P.

Heat in the Treatment of Surgical Shock

QUERY.—Is there any rational basis for the application of heat (by hot-water bottles, radiant-heat cradles, and the like) in the treatment of surgical shock?

REPLY.—A considerable amount of experimental work and clinical observations carried out during the late war showed that excessive heat was harmful in shocked animals and probably also in man. The idea of vigorous heating in the treatment of shock was abandoned, and the recommendation given in the second edition of the Medical Research Council Memorandum on the treatment of shock was that the patient should be given enough cover for comfort, whilst vigorous heating should be avoided.

PROFESSOR J. MCMICHAEL, M.D., F.R.C.P.

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Vitamin D₂ Therapy of Psoriasis and Acne

ALTHOUGH the mode of action of vitamin D₂ in the treatment of skin diseases is still obscure, the highly satisfactory results obtained in lupus vulgaris tempted P. Cerutti (*Minerva Medica*, December 8, 1948, 39, 643) to try this remedy in an oily vehicle in psoriasis and acne. He gave 15 mg. (600,000 I.U.) by mouth three times a week for the first week, twice a week for the three succeeding weeks, and once a week thereafter. He advised his patients to take at least half a litre of milk daily in order to absorb sufficient calcium salts to guard against any possibility of intolerance. Twelve patients with psoriasis were treated over a period of several weeks with completely negative results. In acne vulgaris, on the other hand, the results were most promising. Nine patients were treated, aged between nineteen and twenty-seven: 7 juvenile acne vulgaris of the superficial type, 2 deep acne indurata. All had had various types of treatment without benefit, and none showed any evidence of coexistent tuberculous infection. There was a noticeable improvement after the first four or five days. Three patients—two superficial juvenile acne and one acne indurata—were considered to be practically cured after two to three months' treatment. Four others showed considerable improvement. In only two cases were the results disappointing.

Vitamin D Intoxication

DETAILS are given by J. E. Howard and R. I. Meyer (*Journal of Clinical Endocrinology*, November 1948, 8, 895) of the findings in ten patients with vitamin D intoxication as a result of receiving vitamin D for the treatment of arthritis over periods ranging from two to eighteen months. The daily dose had varied from 150,000 to 600,000 I.U. Weakness, fatigue and lassitude were early symptoms in all ten patients. Loss of weight, anorexia, nausea and vomiting occurred in eight; in none was the vomiting severe enough to produce alkalosis. In seven patients polyuria, thirst and nocturia were present. Intense generalized pruritus occurred in two patients. Nine patients had the characteristic slit-lamp findings in the eyes—deposits of calcium beneath the conjunctival basement membrane and lesions of "band keratitis". All the patients had evidence of impaired renal function; the blood non-protein nitrogen was raised (46 to 106 mg. per 100 ml.) in all; there was albuminuria (mild) in seven; the urine of four patients contained a few casts, and occasional red blood corpuscles were found in the urine. Hypertension, but only slight, was found in four patients. The serum calcium

was raised in all (12.4 to 15.1 mg. per 100 ml.), and anaemia was present in nine. The only treatment given was withdrawal of the vitamin D, "forced fluids" (4000 ml. daily) and a low-calcium diet. Subjective improvement occurred within two to eight weeks, but objective improvement was more variable; for instance, hypercalcaemia was still present in one patient fourteen months after the administration of vitamin D had been stopped. It is also stated that in only two of the patients has recovery been complete. It is recommended that patients to whom vitamin D is being given "should be carefully followed by frequent slit-lamp examination, urinary analyses and determinations of the serum calcium".

Intravenous Procaine in Convulsions

"PROCAINE hydrochloride is reputed to be a convulsant drug", says O. Schmahmann (*South African Medical Journal*, December 25, 1948, 22, 799): "It is here shown that the drug has a marked anti-convulsant effect . . . Dependent on dosage, dilution and rate of administration, exactly the opposite effects can be produced in one and the same case." The case recorded is that of a thirty-four year old male who sustained a compound comminuted fracture of the middle of the frontal bone, in addition to a comminuted fracture of the femur. He was given antitetanus serum, sulphadiazine and penicillin, and the fractures were set. About four weeks later convulsions set in, and in spite of treatment with luminal, seconal, penicillin and a further dose of antitetanus serum the condition deteriorated and the patient appeared to be dying. Procaine hydrochloride was administered, 1 per cent. solution in 5 per cent. dextrose-N saline: 4.5 g. procaine was given in a total flow-time of 18 minutes, including 3-4 minute intervals. Within two minutes there was improvement in the pulse, within five minutes the convulsions were less, and in a further five minutes subsided completely. In all, the patient received 54.5 g. procaine hydrochloride in three and a half days. Antitetanus serum and penicillin were also given.

Treatment of Dysmenorrhœa with Synthetic Antihistamines

THE origin of dysmenorrhœa is still sometimes obscure: there is no organic uterine cause, nor is the origin ovarian; endometrial biopsy shows no signs of disturbed hormonal equilibrium in the folliculo-luteal phase. Nor can such patients be relegated to the group of vegetative dysfunctions. These facts are pointed out by A. Ameline (*Presse Médicale*, November 20, 56, 821) who, on the basis of his observations,

PRACTICAL NOTES

Diagnosis of Brain Tumours

IN an article dealing with the delays and errors in the diagnosis of tumours of the brain, F. C. Redlich, R. H. Dunsmore, and E. B. Brody (*New England Journal of Medicine*, December 16, 1948, 239, 946) give the following list of symptoms complained of in 100 cases of brain tumour verified by operation or at autopsy:—

Complaint	No. of cases
Headache	86
Disturbance of eyesight (amblyopia, amaurosis, blurred vision, scotoma)	36
Gastro-intestinal symptoms:	
Vomiting	32
Nausea without vomiting	27
Seizures	30
Locomotor unsteadiness (falling, lack of co-ordination)	29
Double vision, ptosis	21
Weakness of limbs	21
Personality changes (neurotic complaints)	21
Speech difficulties	19
Dizziness	18
Memory and intelligence deficit	18
Fainting	17
	15
	14
	12
Loss of hearing	11
Incontinence	9
Weakness of facial muscles	9
Psychoses	3
Amenorrhœa	5
Weakness of half one side	5
Stiffness of neck	4
Weight loss	3
Tremor of hands	2
Tilting of head	1
Loss of sense of smell	1

In a survey of diagnoses made by family doctors "only 4 per cent. correct diagnoses and 2 per cent. doubtful diagnoses were made". The most common erroneous diagnoses were "nothing wrong", "neurosis", "epilepsy", and "eye disease". It is pointed out that although in many cases diagnosis was delayed by social and psychological factors "the failure of the practitioner to carry out routine brief neurologic examinations and a tendency to attribute symptoms to personality difficulties with subsequent lack of further investigation seem important". Emphasis is laid on the need for public health education, both lay and professional, to avoid such delays in diagnosis: in half the recorded cases there was a delay in diagnosis of a year or more.

Dextran as a Substitute for Plasma

A REPORT of the use of dextran as a substitute for plasma transfusion at the Serafimer Hospital, Stockholm, is given by G. Thorsén (*Lancet*, January 22, 1949, i, 132). The preparation used was "dextran Ph" (Pharmacia; Sweden), a 6 per cent. solution of polydispersed glycose-polymer dextran with 0.9 per cent. sodium chloride added. In some cases as much as 4 litres per infusion was given; the largest

amount was 10 litres. Results obtained in the treatment and prevention of shock were good. The substance is stated to be non-toxic. A further report on the use of dextran (a preparation supplied for clinical trial by a British firm) is given by J. P. Bull and co-workers (*Ibid.*, 134) of the M.R.C. Blood Transfusion Research Unit, British Postgraduate Medical School. The first trial was carried out on 6 patients with inoperable cancer, who were given infusions of 300 to 500 ml. of dextran over periods of 30 to 90 minutes. No ill-effects were noted apart from rise in jugular venous pressure. Further trial was carried out in a group of 29 patients undergoing surgical operations, the rate of infusion varying from 200 ml. in two minutes to 540 ml. in six hours (slow drip). The results were good, but again it was noted that care was necessary to avoid circulatory overloading. Finally, dextran infusion was used in two cases of severe burns, with good results. In conclusion it is stated: "Dextran has proved efficacious as a plasma substitute in cases of burns, and has produced a sustained increase in the venous return in patients with surgical shock and hæmorrhage . . . it has not been shown to produce any harmful effect on the tissues . . . further investigation is recommended".

Quinidine Sulphate in the Treatment of Hiccup

FOLLOWING the results obtained by the administration of quinidine sulphate to a patient with persistent hiccup which had proved refractory to other forms of treatment, S. Bellet and C. S. Nadler (*American Journal of the Medical Sciences*, December 1948, 216, 680) record its use in eight further cases. Quinidine sulphate was given orally or by intramuscular injection; by the former method in doses of 5 to 10 grains (0.32 to 0.65 g.) and by the latter in doses of 9 or 10 grains (0.6 to 0.65 g.) dissolved in 20 ml. of normal saline solution. The authors suggest as a dosage regime, an initial dose of 10 grains (0.65 g.), preferably by intramuscular injection, repeated hourly for three to four doses, and then, if the paroxysm ceases, a maintenance dose of 5 grains (0.32 g.) every two or three hours with resumption of the initial high doses if there is recurrence. In the treated series the treatment was effectual in 6 cases, in 2 partially successful, and failed in 1 case. The treatment is not recommended for all cases of hiccup, but only for those in which persistent hiccup has proved refractory to other forms of treatment and the continuance of paroxysms results in exhaustion of the patient.

REVIEWS OF BOOKS

Measurements of the Public Health. By F. A. E. CREW, M.D., D.Sc., Ph.D., F.R.C.P.Ed., F.R.S. Edinburgh: Oliver & Boyd, 1948. Pp. xix and 243. Figures 57. Price 18s.

THIS is a fascinating book. If more textbooks were written in this style, the lot of the modern medical student would be much improved. It might aptly be given the sub-title of "vital statistics for the millions". The purpose of the book can be best summarized in the author's own words: "The state of the public health, of the health of our society, is measured and reported on annually by the Registrar-General. . . This manual takes the figures so bountifully provided by the Registrar-General [for Scotland] in his 1945 report . . . and attempts to find their meaning." The subject is covered under the headings of population, birth and fertility rates, illegitimacy, multiple births, the sex ratio, marriage, the biology of death, and stillbirth, infant mortality and maternal mortality. To at least one reader this book has been a revelation of how the intricacies of vital statistics, mutations, genes, multiple births, and the like, can be simplified and clarified without any loss of accuracy. It is no exaggeration to say that this is a book which is essential for every medical student. This is social medicine as it should be, and Professor Crew has set a standard of exposition which it will be hard to emulate.

The Chest and the Heart. Vol. 1 and 2.

EDITED BY J. ARTHUR MYERS, M.D., Ph.D., and C. A. MCKINLAY, M.D. Springfield, Illinois: Charles C Thomas; Oxford: Blackwell Scientific Publications Ltd., 1948. Pp. xv and 1021; xvii and 1846. Figures 430 and 335. Price 7 guineas.

THIS is intended to be an integrated survey of diseases of the chest and heart for both practitioner and specialist. Whilst the scope of the book is certainly wide enough for the practitioner, it is perhaps in some respects too comprehensive; this applies particularly to the part dealing with tuberculosis, which includes no less than 239 pages covering cutaneous, bone, urogenital, abdominal and other forms of tuberculosis which are strictly outside the sphere of the general physician. The first section of the book, devoted to the chest, has been arranged in eight parts; the last part dealing with tuberculosis is unfortunately only partly included in volume I, with the remainder in the second volume. There is an original and interesting chapter on "the common cold", and an excellent

chapter by Dr. McKinlay on "pneumonia"; pulmonary tuberculosis is well presented and the various methods of treatment employed are described with a welcome attention to practical detail. The second section, devoted to the heart, is disappointing; whilst the anatomy, developmental embryology, physiology and radiology of the cardiovascular system are fully described with a wealth of illustrations and reproductions, the clinical section is not sufficiently detailed. No mention is made of the heart in anæmia, and the chapter devoted to the heart in thyroid disease is all too brief for such an important subject. This book will consequently have a limited appeal: mainly as a reference book for those primarily interested in special aspects of chest disease—tuberculosis, chest radiography and industrial or social chest disease.

Modern Trends in Psychological Medicine, 1948. EDITED BY NOEL G. HARRIS, M.D., F.R.C.P., D.P.M. London: Butterworth & Co. (Publishers) Ltd., 1948. Pp. xii and 450. Figures 25. Price 50s.

THE practitioner will find much helpful information in this book, which covers a wide field. The chapters, however, are of rather unequal merit. There is a sound chapter by Whitehorn on simple psychotherapy. M. James gives an up-to-date account of diagnostic measures. There is a good chapter on the psychopathic personality by Stalker, a subject about which more ought to be known by medical men. Moodie provides a well-written account of what a child Guidance Clinic can and cannot do. Palmer gives an informative account of the recent techniques of physical treatment, whilst Bierer discusses the new movements of group psychotherapy and clubs for psychiatric patients. Mental hygiene in industry by Tredgold and rehabilitation by Main also represent recent therapeutic trends. Advances in electro-physiology and electroencephalography are described by Golla. Exceptionally well written are the rather philosophical discussions on the physiology of the emotions by Wright and the causative factors in mental disturbances by McInnes. Personnel selection, by T. F. Rodger describes one of the most important war-time achievements of psychiatry. Harris and Edkins both relate some interesting experiences with abreaction, a phenomenon always considered of therapeutic value. Practitioners may also read Griffiths' account of how it is hoped that Marriage Guidance Clinics will help family life by dispelling ignorance regarding the psychology of sex and marriage. Some of the book, however, abounds in platitudes and

considers the condition to be due to uterine visceralgia. He has carried out treatment with synthetic antihistamine drugs—first with 2339 R.P. and then with neo-antergan. One 0.1 g. tablet is given at the first appearance of pain, followed by half a tablet hourly, swallowed with a drink of bicarbonate in sweetened water. In no case did a total dosage exceeding 0.5 g. (5 tablets) prove necessary. In some cases one course of treatment was sufficient, and the patients remained free of symptoms during an observation period of fourteen months; in others two consecutive courses of treatment proved necessary; and in some, after an apparent cure for eight to ten months there was recurrence, which responded to a fresh course of treatment.

Pyridoxine in Radiation Sickness

In a review of radiation sickness and its treatment, L. M. Shorvon (*British Journal of Radiology*, January 1949, 22, 49) gives a list of sixteen theories which have been advanced as to its causation. Among the many remedies which have been advocated, he mentions adrenaline; corpus luteum, cardiazol and ephedrine; morphine sulphate, calcium chloride and calcium lactate; sodium chloride; sodium bicarbonate; glucose; amphetamine and dextro-desoxyephedrine; desoxycorticosterone; benadryl; liver extracts; and various components of the vitamin B complex. He himself has found pyridoxine most satisfactory, and he gives the results he has obtained in 69 cases. In addition to its value in radiation sickness, stress is laid upon the value of its effect in increasing the leucocyte count. Another useful result of treatment with pyridoxine is the sense of well-being which patients experience. The dosage and mode of administration varied; in many cases five 10 mg. tablets daily were sufficient, but sometimes twice this amount was required. When given intravenously, two ampoules (each containing 50 mg.) were given weekly, but in very severe cases large doses were required. Classifying the results as excellent when there was complete cessation of nausea and vomiting, good when relief was marked but not complete, it is reported that in forty-four cases (63.8 per cent.) the result was excellent, in eighteen cases (26.1 per cent.) the results were good, and in the remaining seven the treatment was ineffective.

Irradiation of Lymphoid Tissue in Respiratory Diseases

SURGICAL removal of adenoids in children is often followed by recurrence of lymphoid tissue in the nasopharynx with consequent return of undesirable symptoms. Such recurrent lymphoid tissue should always be sought for and treated in patients with recurring upper

respiratory disease, otitis media, sinusitis, or impaired hearing due to chronic obstruction of the Eustachian tubes. These facts are stressed by D. F. Proctor, L. M. Polvogt, and S. J. Crowe (*Bulletin of the Johns Hopkins Hospital*, November 1948, 83, 383), who record the successful use of irradiation over a period of twenty-four years at the Johns Hopkins Hospital. The method used is as follows:—

After examination with a nasopharyngoscope, the floor of the nose is anesthetized by the passage of a fine cotton applicator moistened with a few drops of 20 per cent. cocaine. With the patient recumbent, a radium applicator is passed into the nasopharynx on each side of the nose until the end lies against the posterior nasopharyngeal wall in the fossa of Rosenmüller. A timing clock is set for 12 minutes (1 g. 36 sec. equivalent) and the operator goes to a distance of about 20 feet. The applicator is replaced in the nose by the fingers. Two further treatments are given at intervals of two weeks. The applicators used have a radio-active length of 15 mm.

Results obtained from such treatment are (1) improvement in hearing or cessation of progressive impairment when symptoms are due to disturbed Eustachian tube function; (2) marked decrease in the number and severity of upper respiratory infections, including acute infections in the sinuses, ears and tonsils; (3) improvement in many cases of bronchial asthma in children. In conclusion it is stated: "Irradiation of adenoid tissue has now been used for 24 years and many thousands of patients have been treated. In all this time not a single instance of burn or other complication due to the use of radium has been observed".

Zinc and Castor Oil Cream with Compound Tincture of Benzoin

THIS B.P.C. preparation has two practical disadvantages: (1) owing to its excessive greasiness it is difficult to remove from the skin and clothes; (2) in warm weather it tends to separate. To overcome these disadvantages J. B. Hough and A. H. Pryce (*Retail Chemist*, January 1949, 20, 29) recommend the following formula:—

Castor oil	30 ml.
Zinc oxide	7 g.
Compound tincture of benzoin	10 ml.
Lanette wax S.W.	10 ml.
Distilled water	25 ml.
Gelatin solution (3 per cent.)	15 ml.

The Lanette wax SX is melted in the castor oil on a water bath. The distilled water, previously warmed, is then added and the mixture stirred to emulsify. When cool, the compound tincture of benzoin, previously suspended in the 3 per cent. gelatin solution, is added. The zinc oxide is incorporated by rubbing down with the cream in a mortar. If a less viscous preparation is required, the Lanette wax SX can be reduced to 5 g., increasing the water accordingly. It was found that the preparation made according to this formula and method had not separated after six months' storage.

A Way to Natural Childbirth. By HELEN HEARDMAN. Edinburgh: E. & S. Livingstone, Ltd., 1948. Pp. vii and 124. Figures 66. Price 7s. 6d.

THIS short book describes, in considerable detail, various exercises which aim to teach the pregnant woman the art of relaxation. By the complete control of the body thus learned during her pregnancy, an easy and comparatively painless confinement is promised. The book should be studied by all practitioners interested, and actively engaged in obstetrics. Taken in conjunction with Dr. Grantley Dick Read's teaching, it will make the conduct of many of their confinements easier, and for their patients, more enjoyable.

Gynaecological Histology. By JOSEPHINE BARNES, D.M., M.R.C.P., F.R.C.S., M.R.C.O.G. London: Harvey & Blythe Ltd., 1948. Pp. xii and 242. Figures 162. Price 30s.

THIS book accomplishes its purpose. It gives in small space excellent photographs illustrating the histology of most common physiological and pathological conditions of the female genital tract. It does not aim at being comprehensive and the descriptions are essentially simple. The book will prove rightly popular with the candidate studying for gynaecological examinations.

NEW EDITIONS

EDEN AND HOLLAND's *Manual of Obstetrics*, by Alan Brews, M.D., M.S., M.R.C.P., F.R.C.S., F.R.C.O.G., in its ninth edition (J. & A. Churchill Ltd., 42s.) has been extensively revised and much new material added. Three useful appendices deal with diet during pregnancy and lactation, postnatal exercises, and social care of women during pregnancy. This work reflects the teaching and practice of obstetrics at the London Hospital, and the new edition will be assured of a warm welcome.

Clinical Chemistry in Practical Medicine, by C. P. Stewart, M.Sc., Ph.D., and D. M. Dunlop, M.D., F.R.C.P., in its third edition (E. & S. Livingstone Ltd., 17s. 6d.) has been extensively revised. The eleven years that have elapsed since the appearance of the previous edition have seen many advances in laboratory investigations, and this new edition will be found up to date in all sections.

Sexual Disorders in the Male, by Kenneth Walker, M.B., F.R.C.S., and Eric B. Strauss, D.M., F.R.C.P., in its third edition (Hans Hamilton Medical Books Ltd., 15s.), is dedicated to the memory of Sir Walter Langdon-Brown, who wrote the foreword to the original edition in 1939. Among new additions is a short section

on "soldier's impotence". Much stress is laid on the psychic aspects of sexual disorders.

THE ninth edition of *The Clinical Examination of the Nervous System*, by G. H. MONRAD-KROHN, M.D., F.R.C.P. (H. K. Lewis & Co. Ltd., 16s.), which appears only one year after its predecessor, contains among new material a welcome section on electro-encephalography.

Remington's Practice of Pharmacy, by E. Fullerton Cook, P.D., Ph.M., M.Sc., and Eric W. Martin, Ph.C., M.Sc., in its ninth edition (Mack Publishing Co., Easton Pa.; Distributors: Interscience Publishers Ltd., 90s.) has been entirely rewritten. A wealth of new material includes a useful chapter on the antibiotics. This work is a veritable encyclopædia of pharmacy.

"THE function of a Nomenclature is to train the physician to use the clearest and most acceptable diagnostic terms to describe a particular clinical case . . ." quotes Sir Henry Cohen, Chairman of the Sub-Committee on Classification, in his preface to the seventh edition of *Nomenclature of Disease* (H.M. Stationery Office, 8s. 6d.). Since the appearance of the sixth edition of this work the American Medical Association has published three editions of a "Standard Nomenclature of Disease", and although differing in many respects, and particularly in its more elastic etiological diagnoses, the new edition of the present work in some ways adheres to it very closely.

AMONG the new material incorporated in *The Premature Baby*, by V. Mary Crosse, O.B.E., M.D., D.P.H., D.R.C.O.G., in its second edition (J. & A. Churchill Ltd., 12s. 6d.) are sections on umbilical and scalp vein transfusion, new information on epidemic diarrhoea, hæmorrhagic disease, and the extended use of penicillin. The chapter on feeding has undergone thorough revision.

Gadd's Synopsis of the British Pharmacopæia, by H. Whipple Gadd, in its fifteenth edition (Baillière, Tindall & Cox, 5s.), is a summary of the British Pharmacopæia, 1948, and contains information on the poison laws in relation to dangerous drugs and addiction. Its convenient pocket size will appeal to the busy practitioner.

The 1948 Year Book of General Medicine, edited by Paul B. Beeson, M.D., et al. (The Year Book Publishers, Chicago; H. K. Lewis & Co., 25s.) is full of information on recent advances. Among items of particular interest are sections on the use of male Rh-negative blood in the treatment of erythroblastosis foetalis, new measures in the treatment of peptic ulcer, including vagotomy, and a useful chapter on the chemotherapy of infections and specific diseases.

muddled thinking. The section on psychological medicine and world affairs by an American writer, shows a presumptuous attitude that can do psychiatry nothing but harm. Aristotle and Plato are treated with contempt as thinkers. The writer believes that experiments with cats and feeding boxes help to explain international tensions. He thinks Great Britain has chosen an inappropriate time "to be obsessed with a programme of total socialization", and he deplores India's "premature independence". The reader, whatever his political opinions, will perhaps think this strange matter for a psychiatric textbook. The book is marred by such curious mistakes as an allusion to the "hypoglycaemia" of diabetes (which is compared to functional hypoglycaemia), p. 15; Ménézière's disease for Raynaud's disease, p. 54; and Runwell Hospital, "Cheshire", p. viii.

An Introduction to Cardiology. BY GEOFFREY BOURNE, M.D., F.R.C.P. London: Edward Arnold & Co., 1949. Pp. vii and 264. Figures 65. Price 18s.

THIS is an eminently concise and practical textbook which both students and practitioners will find of value. Stress is laid upon the practical aspects of heart disease, and the author has attained considerable success in excluding irrelevant matter. Like so many textbooks based upon lecture notes, it tends to be somewhat stilted in style, but this is compensated for by the tendency towards dogmatism which is so useful to the learner. The sections on treatment are not up to the general high standards of the rest of the book. Thus, it is disturbing to find novasurol still referred to in a textbook published at the present day. Again, to find no reference to the intravenous administration of quinidine in the treatment of paroxysmal ventricular tachycardia is somewhat surprising. Finally, a protest must once again be made against the use of the term, "angina innocens". To label any cardiac neurosis with such a title is tantamount to a life sentence of cardiac invalidism. On the whole, however, this is a useful introduction to one of the more fascinating of the subdivisions of medicine.

Surgery Orthodox and Heterodox. BY SIR HENEAGE OGILVIE, K.B.E., D.M., M.Ch., F.R.C.S. Oxford: Blackwell Scientific Publications, 1948. Pp. vii and 241. Price 12s. 6d.

IN this volume Sir Heneage Ogilvie has collected together twenty-one of his less technical contributions to medical literature. The majority are addresses which he has delivered at various times during the last twenty years. Sir Heneage,

like so many outstanding surgeons before him, is a brilliant dialectician, and these essays are a joy to read, particularly when the reader most violently disagrees with them. Whether they deal with "the training of a surgeon", "the American surgeon", "misleading leading symptoms", or "surgical handicraft", they are always stimulating—and often provocative. Self-assurance, as opposed to smug self-satisfaction, is an essential constituent in the make-up of the successful surgeon. This and a zest for life are the predominating characteristics of these essays. The temptation to quote is almost irresistible in reviewing a book such as this, but limitations of space preclude more than one: "Surgery thus attracts the man whose interest in medicine is humanitarian rather than scientific, who loves his fellow men, who wishes to help them and to see that his help is effective. It appeals to the craftsman . . . to the artist . . . to the romantic . . . to the extrovert. The president of the residents, the footballer, the mountaineer, the yachtsman, are drawn instinctively towards the surgical side of practice. The prizewinner, the editor of the hospital journal, the debater, the naturalist, tend to find their vocation in medicine." This is a book to be read and pondered by all who care for the ideals of medicine.

Joseph Lister the Friend of Man. BY HECTOR CHARLES CAMERON, M.D., F.R.C.P. London: Wm. Heinemann (Medical Books) Ltd., 1948. Pp. 180. Illustrations 13. Price 17s. 6d.

LISTER has been well served by his biographers, but this "intimate biography" will be welcomed by all who are interested in the pioneer of antiseptic surgery. Written by a distinguished son of a distinguished father, Sir Hector Cameron, who was one of Lister's closest friends, it provides a picture of Lister which no official biography could provide. Emphasis is here laid upon the man rather than upon his work, and Dr. Cameron has happily taken full advantage of his unique opportunities of obtaining first-hand information of his subject. Making full use of his father's memories of Lister, the correspondence between the two men, and his own personal memories of occasional meetings in his early days with Lister, Dr. Cameron has succeeded in steering a mid-passage between uncritical adulation and the modern craze for submitting great men to crude psycho-analysis. His is a portrait which brings Lister vividly to life, and he has placed us all under a debt of gratitude for having taken the opportunity, in the course of a busy professional life, to place on record his own, and his father's, memories of "the friend of man".

THE PRACTITIONER

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NOTES AND PREPARATIONS

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NEW APPARATUS

THE "SOLUX" LAMP (Model H.VI) is a new portable unit for infra-red irradiation. This model, which has been devised for the use of practitioners and masseurs as a portable unit, and for patients who need a radiant heat or infra-red lamp for home use on medical certificate, is available in two types: the table type, price £11 to £12 15s. od., and the stand type, price £12 to £13 15s. od. (Hanovia Ltd., Slough.)

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NUFFIELD FOUNDATION MEDICAL FELLOWSHIPS

APPLICATIONS for awards of medical fellowships in 1949, which now include all fields in medicine (see *The Practitioner*, November, 1948, 161, 436), should be received by the Secretary of the Nuffield Foundation, 12 and 13 Mecklenburgh Square, London, W.C.1, not later than April 1, 1949.

CARD INDEX OF NEW PRODUCTS

WITH the object of supplying up-to-date particulars of new pharmaceutical preparations the *Pharmaceutical Journal* has introduced a service of cards giving details of composition, clinical

indications, dosage, references to literature, pricing and price, and the suppliers. This excellent service is available by annual subscription of 5 guineas, and includes a filing drawer. (*The Pharmaceutical Journal*, 33 Bedford Place, London, W.C.1.)

PUBLICATIONS

The British Red Cross Society "Junior First Aid Manual" (2s. 6d.) has been prepared for visual teaching of first aid to young people. It is delightfully produced and should make the study a pleasure. (British Red Cross Society, 14-15 Grosvenor Crescent, London, S.W.1.)

The Home-Help Organiser is the official organ of the National Association of Home Help Organisers. It is a monthly issue which it is hoped will provide a link between all interested in the administration of the Home Help Service. The annual subscription is 3s. including postage. (The Editor, the Home Help Organiser, 31 Margaretta Terrace, London, S.W.3.)

OFFICIAL REPORTS

Department of Rheumatic Diseases, West London Hospital. In addition to the Annual Report for 1948, the articles include a paper "The Rheumatic Diseases in the Eighteenth Century", by W. S. C. Copeman, F.R.C.P., which will be read with interest.

National Association for Mental Health.—The Annual Report 1947-48 is available on application to the Secretary, 39 Queen Anne Street, London, W.1.

National Institute for the Deaf, Annual Report 1948, contains a report of the speech of the Minister of Health at the Annual General Meeting, in which he discussed the Government Hearing Aid. (The Secretary, 105 Gower Street, London, W.C.1.)

Rehabilitation and Resettlement of Disabled Persons (H.M. Stationery Office, price 9d.) the second report of the Standing Committee. It is illustrated and admirably demonstrates the many activities at the different rehabilitation centres.

The Empire Rheumatism Council.—The 1948 Annual Report 1947-48 contains particulars of the Annual General Meeting and the opening speech of H.R.H. The Duke of Gloucester, President of the Council. (The Secretary, Tavistock House (N), Tavistock Square, London, W.C.1.)

The contents of the April 1949 issue, which will contain a symposium on "The Problem of Adolescence", will be found on page lxxviii at the end of the advertisement section.

THE PRACTITIONER

No. 970

APRIL 1949

Volume 162

THE PROBLEM OF ADOLESCENCE

By SIR FREDERICK OGILVIE, M.A., LL.D.

Principal of Jesus College, Oxford; formerly Vice-chancellor, Queen's University, Belfast.

A CANON of the Church was asked recently to give an address to a youth conference. He hesitated. "What can I say to them", he said, "except that I hope they will soon grow up?" Many of us, like the Canon, are self-conscious about young people. We regard them as something awkward, spotty, unpredictable. We are sorry for them. We ticket them "adolescents", like a class apart. We know where we are with children and grown-ups, but oh those bewildering creatures between! Have they really got to be like that?

Adolescence certainly is a problem, and *The Practitioner* has done well to draw wide attention to it in this number. The articles which follow are by experts, and deal professionally with various important aspects of the problem. But they are of high value to laymen also. Adolescence is not only, or even mainly, a problem for professionals. It is a problem which concerns us all, and in some ways all of us are responsible for it.

Where, for example, is blame to be laid for the aspect of adolescence discussed by Mr. Henriques—juvenile delinquency? The latest figures announced by the Home Secretary last month show that, for the year 1948 in England and Wales, 26,715 boys and girls under the age of fourteen, and 16,991 aged fourteen to seventeen, were found guilty of indictable offences and dealt with in magistrates' courts. The corresponding figures for 1947 were 21,152 and 13,861, the year 1948 thus showing increases of 26 per cent. and 23 per cent. over 1947.

No doubt statistics of this kind are crude and can easily be misleading. But in general it is a sombre picture. Who is responsible for it? In part, of course, the young delinquents themselves. It would be grotesque if adolescence came to be so professionalized a study, to be so much thought of in terms of chemistry or glands, that no room was left for the adolescent himself with a responsibility of his own for his actions. But behind the delinquents, what? How many of them come from homes where marriages have been broken, or where parents and neighbours snarl and nag and bully, or spend the day in drink and gambling? How many have had their first taste of delinquency from the talk or practice of grown-ups, in real life or the films? What chances have some of them had of open skies or beauty

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THE ADOLESCENT BOY

By WILLIAM MOODIE, M.D., F.R.C.P., D.P.M.

Physician in charge, Department of Psychological Medicine, University College Hospital.

THE change in personality known as adolescence usually takes place while the body is undergoing the development of puberty. Physically the child becomes a fully functioning sexual adult and at the same time the mental outlook alters, not only towards sexual things but in many other ways. The sexual change is so obvious that it often obscures these others, but they are quite as important. The attitude towards life and the world in general, the nature of thought, the adjustment of personal relationships within the family and to the community, are some of the more important of these.

PHYSICAL CHANGES

The physical changes in the female at puberty are more obviously sexual than in the male. The development of the breasts and the establishment of menstruation have no counterpart in the male sex. In spite of this, however, there is in both a sudden increase of self-consciousness, and the boy is affected by this as much as the girl. This awareness of self depends upon a growing realization of being a separate person with an individuality and characteristics of one's own which constitute the difference between the self and others of the race. Before this self-consciousness develops, the child does not see himself as an individual as much as just a boy, belonging to a family with parents and perhaps brothers and sisters, and one among all the other children with whom he mixes.

Although the bodily changes in the boy are not, in fact, such as to draw any particularly embarrassing notice to himself, self-consciousness accentuates his awareness of his clumsiness, his breaking voice, and his growth of facial hair, and there are often sensitive feelings about things like social habits and clothes. The boy likes to think that he is dressed like his fellows, and shrinks from being differently arrayed. This may extend to other members of the family, and he becomes acutely conscious of how his father or mother appear in public, and of their manners and general bearing. The less obvious he and his family appear through difference, the happier he is. Sometimes there develops the opposite tendency, a desire to differ, but this is not normal and usually betrays an inward feeling that there is something wrong with the adjustment of the personality, from which the boy desires to escape.

Excessive self-consciousness of the external signs of puberty is often associated with feelings of guilt, as if these disclosed to the world at large the secrets of the mind and conscience. Undue shame about acne commonly

or fun? Future historians may well be surprised, not that adolescence was a problem in the middle of the twentieth century, but that on the whole it was so little of a problem.

Above all they are likely to criticize our educational system. They will recall the long struggle for raising the school-leaving age. They will note that it was not until the second world war that legislative steps were taken to keep children at school beyond the age of fourteen. How astonishing, they will say, that the British people before the Butler Education Act of 1944 should have gone on, year after year, throwing their boys and girls out of school, and straight into street or field or factory, at the most critical point in adolescence, and yet should have complained, year after year, that some of their adolescents were a problem to them!

Important as are the medical aspects of adolescence, the problem itself is at bottom social and educational. In Britain until recently there was a marked distinction between two types of adolescent. On the one hand there was a minority, mainly well-to-do, who stayed at school until the age of eighteen or nineteen and whose adolescence was perhaps unduly prolonged. On the other, there was the vast majority who left school as children of fourteen one day, and the next day plunged without a break and without training into an adult world, with adult practices, adult standards, adult language. If they had an adolescence, it was physical only: socially and educationally it had been squeezed out.

With the general raising of the school-leaving age, and with the growth of public assistance for education, this particular distinction between the well-to-do adolescent and others is losing significance. All adolescents now stay at school until fifteen, and soon they will stay until sixteen. The loss of knowledge and skill which often follows within a short time of leaving school was shown, for example, by the incidence of illiteracy in the Army during the war. It is serious from two points of view. An adolescent may be indifferent at the age of sixteen or seventeen to what he has lost, but he himself may have cause to regret it bitterly three or four years later. And, secondly, it is not this or that piece of school learning which it is important to preserve. It is rather the habit of reading and thinking and discussing, of applying rational principles to everyday affairs. Both the personal efficiency of the individual and the well-being of the country demand that this habit should last through life.

With a wise use of the provisions of the new Education Act, with healthy limits to the hours and kinds of work which adolescents may undertake, with proper facilities for recreation, with religious and moral forces making their supreme influence felt, the time may come, and sooner than we think, when adolescents will hardly be a problem any longer. The time may come when they will mostly be talked of again as boys and girls, and adolescence itself will ordinarily be regarded as the glorious and exciting business of growing up.

that there can be little doubt that every mind has many of these loose irrational guilts in the background. They often emerge at adolescence and, when they do, they complicate the dawning appreciation of ethical and moral values.

THE PERIOD OF TRANSITION

During adolescence there develops an intimate, individual impact on adult reality. Where previously the boy has had someone as an intermediary between himself and the world around, he now has to face it personally and immediately. Parents no longer form that buffer which softens, tempers, and interprets the difficulties, problems, and obstacles of the world of *mature people and real situations*. This transition is a tricky process, and its success or failure depends greatly upon how well the boy has been prepared for it by personal experience in the community of children in which he has learned to give and take and to find his place, and also upon the kind of example in living which he has seen in practice. This must be the responsibility of his parents and teachers. The boy who from force of circumstances is deprived of adequate adult protection, guidance and example approaches adolescence unprepared. He has been compelled to look after himself as well as he could when he was too young to make better than a childish attempt to deal with life, and either he recoils from it, remaining immature and ineffective in his attitudes and social adjustments, or his adolescence will bring with it a blind aggression. This is often the basis of delinquency.

Although basic intelligence, that is pure reasoning power, ceases to develop about the age of sixteen, adolescence is accompanied by many important developments in the intellectual sphere. The moment when these occur, and their nature and extent, will show just how the individual faculties and capacities are likely to crystallize and what sort of a fully fledged personality will emerge. The general tendency is towards more complication in the thinking processes. The immature are known as simple-minded, a recognition that simplicity of thought should be left behind as development proceeds. The simplicity which is discarded is the taking of things at their face value, and the consideration only of their obvious meaning, and in its place there develop more abstract conceptions, with a multiplication of associated ideas. To the young child, a chair is "something to sit on", but the adolescent faced with the same question is at a loss. He knows, of course, many different designs of chairs "for sitting on", but he thinks also of the chair at a meeting, chairing the winner of a contest, a chair holding the railway lines, and his mind may run on to a visit to the dentist, or the hairdresser's, or the coronation, or along a hundred and one associations which his own particular personal experience may have imprinted on his mind. This is a relatively definite and concrete example, and if as a starting-point something less tangible is taken, an even more complicated reaction follows.

arises from a belief that it is caused by masturbation. Adolescents often imagine that they betray their thoughts in their facial expression. This idea that others can divine their mental secrets is so common that it must be accepted as part of normal adolescence. Only if it persists need it cause any anxiety, or if it assumes such prominence as to become a delusion that the thoughts can subconsciously influence, or be influenced by, others.

MENTAL DEVELOPMENT

Adolescence brings with it many important changes in the nature of the thought processes. To the young child the world is made up of concrete things and people and he takes it all very much for granted. There is in his mind little speculation as to their nature or origin. They exist, and are part of his world, and he accepts them at their face value. As time goes on, however, he begins to wonder about them. First he wants to know what is inside things—why they go, and how they are made, and then this thirst for information extends to life itself. He is surrounded by the mystery of whence, why, and whither, and some answer must be found for his questioning mind. The depth and detail of the explanations necessary to satisfy this desire for knowledge vary with the age and the mental competence of the child concerned, and also with the degree to which his imagination has been aroused by experience or teaching. This is especially important in sex and procreation. If these are presented to the young child in too great theoretical detail before he is capable of understanding, it is likely that he will develop mental barriers which will make it harder for him to accept the facts when he should normally be ready to do so.

The natural interest and emergence of *understanding of sex* at adolescence is greatly influenced by this early teaching, and also by prohibitions, condemnations, and threats made to the child in his earlier days. For example, fears of madness, blindness, or future impotence are all too frequent in adolescence, as the supposed penalties of early sexual pre-occupations. The growth of consciousness and understanding brings an awareness of past impressions thus associated with sin or its consequences, and neither the reason for these nor the connexion between them is understood, so they form in the mind an incoherent load of unhappiness and anxiety. These difficulties are so common in the shut-in adolescent that they must be considered part of his normal make-up.

Profound feelings of guilt are universal in the background of neurotic illness, guilt nominally attributed to consciously remembered acts, but obviously severe and disproportionate to the "wickedness" of the acts to which it is attributed. Investigation invariably reveals that this guilt is really derived from past incidents for which the child was reproved and called naughty or wicked—incidents of which he was at the time unable to appreciate the evil, and the load of ununderstood guilt has attached itself to incidents or habits which give an excuse for guiltiness. This is so common

The tie between the two, however, is not broken, but only altered in quality. Companionship takes the place of dependence and control. This is fundamentally natural and proper, but often the process is complicated by emotional disturbances which make it awkward. The boy's attempt to break away may be obstructed by over-possessiveness on the part of the mother, or he himself may be unwilling to relinquish his position as the protected child. The degree to which these attitudes block the normal course of development depends upon whether the mother-child relationship has previously been normal, or whether one or the other, or both, have grown abnormally dependent upon the other because of deprivation of emotional outlets in other directions. Again, the smooth working of this emotional evolution will depend upon earlier training and experience.

The boy's attitude towards his mother at this time usually has some effect upon his relationship with his father who, in his turn, will respond to the situation in his own way. Jealousies may arise as a result of competition for the mother's affections, or the father may feel that the mother's solicitude is obstructing his son's emotional development, keeping him childish and preventing the growth of a more mature male companionship between the boy and himself. Very often these jealousies are the origin of apparent antagonisms among parents and children.

Although the mother-son relationship in adolescence need never display signs that can legitimately be called sexual, it plays an important part in the change from the relatively sexless state of childhood to that of full functional sexual maturity. During the period of transition, the sexual instinct is evolving. This is a gradual process, and so the impulses, urges, fantasies and experiences are only gradually appreciated, coordinated and controlled. If, while they are developing, these powerful, elemental, instinctive forces were not kept under control, anything might happen, and it is during this time that attachment to the mother gives a blunting of the desire to indulge in experiment and indiscriminate activities. The completion of adolescence brings an end to these protective inhibitions.

Masturbation is so common in adolescence that it must be considered normal. In moderation it does no physical harm, but in excess it is an indication of emotional disturbance, or even of mental disorder. There is no hard and fast line between the occasional practice, which is in itself harmless, and excessive indulgence. Useful indications are the extent to which guilt accompanies the act and the degree to which it is associated with vivid fantasies of coitus. Sometimes it is dependent upon obsessional compulsions. As a general rule, in the normal boy, the only important feature is the guilt the act arouses. Otherwise it is of little importance, although it may be an indication of introversion.

THE ATTITUDE TOWARDS AUTHORITY

An important development of adolescence in the social sphere is the nature

There is, everywhere about us, evidence of man's search after the spiritual. Even when the existence of *religion* is denied, the very denial is ever present. In most countries it is impossible to walk in any inhabited locality for more than a few moments without seeing a church, or some other religious emblem. There are many people of standing and of wisdom who practise, or at least accept, religion as a reality, and there are many more who give lip service to it as a habit, or perhaps only because they feel it "is a good thing". Prayers are offered daily in schools, and there is often, too, some instruction in Divinity. Many parents bring up their children to take for granted that there is a spiritual background to life. The early questions about who or what God is come naturally out of this vague background, and it is inevitable that when the mind begins to stop taking for granted and begins to think for itself, these early impressions come under review. How they evolve will depend upon how objectively, maturely, and deeply the mind has learned to think. The transition from factual to abstract thinking is always difficult, and the conflict arises as to whether security will be sought from some scientific theory, such as evolution, to the exclusion of undemonstrable spiritual conceptions, which may be disturbing, or whether the whole question will remain *sub judice*, gradually to evolve and define itself in the light of later knowledge, experience and observation, which is more healthy. Sometimes a blind acceptance of mystical religion comes in a violent emotional flood. Sin and guilt are linked with judgment and eternal damnation. This fear of an omniscient and avenging Power is not uncommon, and need not necessarily presage mental disorder. It arises at adolescence if the introvert type of personality has been over-stimulated by emphasis along these lines. In this, as in other directions, the attitude adopted will be determined partly by the inborn constitution, but to a greater extent by the influence of the environment.

PARENTAL RELATIONSHIP

An important factor in adolescence is the emotional relationships between the boy and his parents. Much has been written about the "œdipus complex", how the boy has in his unconscious mind repressed sexual desires towards his mother. In the course of deep and prolonged psycho-analysis this complex often emerges, but it is doubtful if it is, in fact, normally present in the intensity and to the degree in which it exists in pathological cases. Even if the theory be accepted that the œdipus complex is always present, it is clear that if this be so, it is ordinarily repressed completely. Repression is the mind's natural way of dealing with intolerable antisocial impulses.

Be this as it may, one of the common accompaniments of adolescence is a modification in the emotional relationships between the boy and his mother. Not only does he cease to need her constant care and protection, but he begins actively to resent it. He is now grown up, and can look after himself.

THE ADOLESCENT GIRL

By WINIFRED RUSHFORTH, M.B., CH.B.

Medical Director, the Davidson Clinic, Edinburgh.

THE adolescent girl differs from her sister, still in the latency phase, i.e., between the fifth and twelfth years, in a remarkable degree. Her appearance has changed; slim straight lines have given place to curves. A year or two of age has meant rapid increase in height, girth and weight. The onset of the menstrual flow is a dramatic event in the girl's life, a sharp cutting off from childhood and entrance into woman's estate. Psychologically, there is not only this dramatic change initiated at puberty but also the long drawn out processes that go on during as much as ten years or longer while the rhythms and tides of the woman's life are established. It is indeed fashionable nowadays to label certain types "adolescent" even in their old age.

PERSONALITY CHANGES

The structure of the personality alters in at least as startling a manner as the configuration of the body. The condition has been likened to the chrysalis stage in the life of the winged insect. The adolescent withdraws into an isolation and self-consciousness, comparable to the isolation in the cocoon. A process of disintegration occurs, comparable to the "liquidation" of the caterpillar. This is followed by reintegration (the growing of the wings) and emergence into the human being of civilized type, aware of non-material values (the taking wing into a new element).

It may be noted in passing that adolescence is an affair of civilization and of the more definitely psychic or spiritual aspects of life. Pre-human mammals (the great apes) come to maturity and reproduce their kind at the age of five, when man is still an infant. Primitive men and women reproduce soon after the age of puberty. Adolescence is a gift of civilization; it is lengthened when there is a long era of peace, and is at once cut down for both men and women when war is imminent or actual. Adolescence has something of the nature of a second infancy. The instinctual life is making renewed efforts to establish itself and free itself from the control of parents or parent substitutes. The infantile sexuality, which is so much a matter of fantasy in the early years, has lain dormant through early school life, but is now active again, greatly reinforced by the presence of ovarian secretions in the blood stream.

The first phase of isolation is connected in some way with the development of modesty and shame. This may have to do with the concealment of menstruation. It is noticeable in girls (other than those who mix in boarding schools or in other community circles) that each girl is likely to think her body ugly or offensive. The pubic hair may be thought of as an individual blemish. The breasts may be considered ugly, and even the feet or hands

of the attitude towards authority. This has two main components. There is a tendency to resent and resist control, and at the same time a desire to shelter behind it to avoid increasing responsibility. An important aspect of character depends upon how the balance between these is adjusted. It is clear that resentment of control must be the resultant of what the boy wishes to do, and the extent of the latitude he is allowed. It is in this that the effect of early discipline and training lies. If childhood is remembered as a long series of curtailments of freedom, then the adolescent will find it more difficult to face outside reality with confidence and a sure grasp. Sometimes he tries to rebel, but this is seldom successful, and usually he turns more and more towards inner sources of satisfaction. If, on the other hand, he has been given too much freedom, which usually goes with too little help and guidance, he will attack his problems with only that experience and knowledge which he has been able to acquire unaided, and secretly fearing them, he will be aggressive, intolerant and uncooperative.

CONCLUSION

Adolescence is the brink of life, and a boy can effectively and comfortably graduate from his childhood only if he comes to it soundly equipped from his earliest years. The process is not easy, but it is part of the life experience of us all. It is the testing time, and throws into relief any flaws in earlier training. Fortunately the average child is normal and resilient, and the average parent is wise enough to bring him up satisfactorily, and so adolescence, with its strange metamorphosis, usually passes naturally, although in the process it may sometimes seem that strange things are about to happen. On this account it is wise to adopt an expectant attitude, and not be too deeply disturbed by superficial appearances. Many a turbulent adolescence is, in fact, only evidence of a temperamental adjustment, through which earlier troubles are being satisfactorily solved.

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may take on an aspect of shamefulness so that they cannot be displayed. Community life, of course, breaks down this isolation so that a reversal may take place. Modern maidens compete with each other in the achievement of puberty, and the chatter of changing rooms gives a sense of inferiority to those whose menarche is delayed. It is noteworthy here to observe how inferiority finds an excuse to assert itself in adolescence, attaching itself to anyone who differs from the crowd, be it in truth or in imagination. To be "one with the others" in size, in shape and in feeling makes for happiness, whereas to be "odd man out" makes for distress and feelings of rejection. An only girl in a family of boys suffers more particularly in this way at this period of her life. She is different, and the differences become more marked each day. Even if the brothers are kind she feels rejected. Barriers of incest-prohibition are growing inevitably but there are no words to express the emotions involved. It is happening largely in the unconscious and is often rationalized in bitter quarrels and resentment, all increasing her isolation and unhappiness.

The disintegration of the personality in the adolescent girl gives rise to situations in which there is enmity between herself and society. The childish patterns which tend to culminate in good behaviour during the early school age (5 to 12) begin to break down. The disrupting forces are the instincts of sex and aggression, very closely linked in the unconscious, now reinforced by the endocrine development. Turbulence, delinquency, disregard for adult conventions are the evidence of this breakdown. The outer world in the shape of parents, teachers, society at large is apt to be shocked and horrified. The inner world of the girl's own conscience and idea of herself is equally dismayed. The disintegration is of all degrees of severity. It may only be obvious as moodiness and bad temper; it may issue as a complete split, schizophrenia—the affliction of adolescence so common to-day.

In all probability the conditioning of these conflicts of adolescence is to be found in infancy, which is also a time of conflict. If the stresses of infancy are repressed rather than resolved they lie latent, ready to re-emerge with violence at this time. An example is to be found in infantile masturbation. A little girl, during the early months of life, explores her body, fingers and toes, as well as all the orifices which are charged at that time with erotic feeling. If she is a happy child, with plenty of relationship to people and things, her own body will be only of passing interest and she will have her own wisdom of "moderation in all things". An unhappy child, without relationship, even it may be without toys (such for instance as may be found in institutions) will seek her own bodily sensations with greedy violence and without moderation. In either case disapproval and direct interference will set up conflict. Either side may win during infancy, but the battle will begin again, if it has ever stopped, in adolescence and may now be so severe as to cause a split in the personality. The conflicts and griefs of infancy are terrible things, but less obvious and spectacular

than the turbulence and delinquency of adolescence. It is well to bear in mind that just as the aggression of infancy comes to a height at about the third year and then passes, so also the violence of adolescence if handled aright can work itself out as creative activity and community service.

Reintegration is the third stage to be observed in adolescence. The personality tends to come together again, the split tends to heal. An important factor in this healing may be an identification with an older woman. Sometimes the mother may fulfil this function but more often barriers have arisen and some other woman, a schoolmistress, some friend in the factory, a club-leader, or it may be an officer in the Services takes her place. Probably the barrier arises, in part at least, because of the mother's unwillingness to impart sexual knowledge—this factor operating from the very earliest questionings of infancy. In fortunate cases the mother has kept herself accessible to the daughter's need for knowledge, and allowed her child to establish the identification so that "we women" share in the mysteries. When, for some reason or other, the mother-daughter relationship has become a bad one, then there is great need for a mother-substitute who can handle the situation wisely. Reintegration may largely depend upon the establishment of a temporary relationship of this kind, giving a necessary measure of security. As the isolation and disintegration give way, groups are formed which also make for security. They are in the first place markedly homosexual with a certain defensiveness against the males, but this breaks down as heterosexuality develops. It matters very much to girls in their later teens that they should have ample opportunities of meeting boys in fair numbers, otherwise the homosexual phase persists too long and may never be broken down.

THE PARENTS IN THE MANAGEMENT OF ADOLESCENCE

The part played by the father in his daughter's development may be considered here. If he has taken his share in family life during her infancy she has in all probability established him in her imagination as the perfect man. Three-year old daughters and their fathers are very often all in all to each other, and little girls miss their fathers very badly when they are away from the home or have died. Perhaps the maximum need for the father is at this tender age in his daughter's life; he supplies something that the mother alone cannot give. Father and infant daughter have a symbiotic value to each other: she eliciting his fatherhood, he stimulating her capacity for love-making to be brought into action when she becomes a grown woman. In the middle years of adolescence this is reawakened and a mimic love affair may be enacted between father and daughter. If the original mother-father relationship stands firm then this affair can be played quite prettily, provided that the father is conscious of what is going on and does not let it become too actual. Adolescent girls should not sit on their father's knees, nor is much kissing or fondling advisable. The daughter's privacy in her bedroom should be respected. Housing difficulties which deny adolescent

girls their natural demands for segregation from the men of the family are a great cause of disaster in peoples' lives to-day. Girls at this age are very sensitive to the quality of the relationship between their parents and are often critical of their mother's lack of skill in managing the father or of the father's foolishness in being dominated by his wife! This makes inevitably for friction between the girl and her mother, which is not easily dealt with.

In many primitive civilizations the boys and girls are separated from their parents at puberty and encouraged almost immediately to undertake the responsibility of reproduction. There is perhaps biological sanction for the teaching that parents are not the best people to manage their adolescents, and that indirect rather than direct management of the situation is advisable. The parents, for instance, may well take notice of their own marriage and see if it has fallen into disrepair, since it is such breaking up of relationship that makes the daughter tend to become fixated on her father. A fresh common project of some sort might be helpful in uniting them again. It is also true that by the time the family is adolescent the mother should be free to occupy herself anew with some interest outside the home which will prevent her from becoming dull and uninteresting. It is good, too, that as the father ages he should have hobbies or enterprises which will absorb his creative impulses, and leave him less leisure for his daughters.

Probably parents are wise who thrust their daughters out into the world at this stage, and who allow them to meet as wide a range as possible of people of all ages. Among these are likely to be some older women who will possibly cause the mother some feeling of jealousy. For her growth it is good that the daughter should make such friends, thus giving her cultural interests or it may be religious or psychological teaching not available in the family. It is likely also that she will meet men of different ages. The father perhaps tends to be slightly deprecatory in his attitude to the youths of her own age, but the alliance with such is a much sounder proposition than relationship with an older man.

SEX EDUCATION

Adolescent girls of to-day are much better off than their mothers or grandmothers were in the matter of awareness of sexual relationship, particularly in the better educated classes. The cinema leaves something, if not much, to the imagination, but it must be remembered that repression still acts, as it has always done, and that many girls in their teens have surprisingly little clarity in their sexual knowledge.

It is now generally accepted that information about sex should be given in the following ways:—First, in early childhood, when in answer to questions simple but truthful statements of fact should be made. The necessary information should include a description of the different formation of male and female bodies, the facts of growth of the babe in the mother's body, of the giving of the sperm by the father in intercourse, and of the way in which

the babe is born from the mother's body. In the second place, school teaching should describe objectively the various functions of the body, including reproduction. Thirdly, more subjective teaching is necessary in adolescence, the mother or some mother-substitute establishing the attitude of "we women" and being willing to describe again the facts (they are surprisingly often forgotten or repressed). Discussion should be encouraged as well as the eliciting of what the girl thinks and knows. Before the onset of menstruation it is necessary to talk about what will happen. The anatomy of the woman's body should be made clear at this time, either through diagrams in books or, still better, by drawing simple diagrams or making models. Obviously, questions will also be asked and need to be answered about the opposite sex. Very often in the psychotherapeutic clinic we find that a delayed menarche is due to lack of knowledge or fantastically inappropriate ideas about menstruation. There is often quite a dramatic change of expression and attitude in a girl patient who is initiated with kindness and with understanding into the facts of her womanhood, and menstruation may then begin within a few weeks or even days. Probably girls should always be initiated by women, as menstruation is so definitely a woman's business that through the ages has been hidden from men. With the good intention of protecting them from danger, many ignorant women threaten their daughters with terrible disaster if they permit intimacy with men, even warning them never to allow a man to touch them! Undoubtedly this threat given at a time when the girl is emotional and sensitive causes great fear. Such a fear is not easily dealt with and may give rise to disturbance in the subsequent sexual life of the daughter, causing abnormalities in menstruation, frigidity in intercourse, and even difficulties in childbirth. Undoubtedly, the giving of sexual information by the mother to the daughter, when accomplished in a wise and tactful way, helps to establish good relationship between them and lessens the risk of psychic trauma should the girl have the misfortune to be exposed to an exhibitionist or to other distressing aspects of sexuality.

The cinema and certain aspects of radio and of literature have an overstimulating effect upon girls, so that a premature development takes place often characterized by shallow sentimental feeling and a lack of real knowledge or understanding of what life involves in the way of responsibility. The magnitude of this problem is extreme, and the difficulty of protecting the adolescent from the entirely false values of Hollywood confronts and dismays all whose insight enables them to assess the damage done. Youth centres, playing fields, clubs—all such facilities organized by men and women of character and giving scope for the meeting of both sexes—are at any rate possible ways to present a more real chance for life to develop satisfactorily.

Adolescent girls suffering from intensification of the normal processes of isolation and disintegration are often in need of help such as is offered by psychotherapy, but they are notoriously difficult to approach. Psycho-

therapists often refer to them in despair as clams or oysters into whose shell they cannot penetrate. Still these youngsters seem to like the atmosphere of the clinic and in some cases, at least, they like to do handicrafts, or to paint pictures, or relate their dreams, through all of which approaches some access is gained. Often they will seem grateful for systematic teaching about sex, and in default of other approach it is good to give this teaching. It lessens the sense of isolation to have matter-of-fact talks about the bodies of men and women and the sexual functions. Girls at this age may be very guilty about masturbation and the tension can be eased by talking about it without any condemnation. If the girl is in difficulty and is living with her parents it is often a good policy to approach the parents (whichever is accessible, usually the mother) by psychotherapeutic methods.

PSYCHOGENIC DISORDERS

In a wide range of disease and disorder in adolescent girls psychogenic factors are discoverable, and with surprising frequency the discovery of such factors leads to cure. Possibly every adolescent is living in conflict between the urges towards, on the one hand, creativeness, involving the rough contact with the outside world, and on the other hand, regression, the return to security and comfort to be found in illness. Traumatic influences in pre-adolescence may determine a delay in development showing, for instance, as primary amenorrhœa or affecting any one of the other systems. The urinary system responds with enuresis or with, what is perhaps equally common in girls, compulsive urination, leading to wetting of garments. The alimentary system may show anorexia, vague gastric disorders, constipation or certain forms of diarrhœa. The locomotor system may be affected by chorea or by rheumatism; the skin by different disorders—acne, eczema, psoriasis; the nervous system by functional paralyses; the vasomotor system by excessive blushing and sweating; the pulmonary system by asthma and bronchial disturbances.

Apart from physical disorder there is a wide range of *behaviour abnormality*. At one end of the scale this is only manifested by critical or hostile attitudes to parents and parent-substitutes; at the other by full-blown delinquency on a large scale.

CONCLUSION

Parents are apt, perhaps, to be unduly distressed and alarmed by the natural processes of isolation and disintegration, and the family doctor can do much by reassurance of the parent and by urging toleration of these processes. When parents are anxious and possessive the situation demands tactful handling and the mediation of one who understands both sides is invaluable. The parents may be tactfully reminded that their day of influence is largely past. At this stage the girl needs freedom rather than security, encouragement rather than threats and warnings. She must be allowed to leave behind her the phase of being the good daughter and enter into her womanhood as wife and then mother, so completing her emergence from adolescence.

THE "DELICATE" ADOLESCENT

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EVERY doctor who has to deal with adolescents is familiar with the child who is presented to him as being "delicate". We may perhaps define this child more precisely as one who, without a diagnosis of any specific disease, is considered unfit physically to live the full active life of adolescence. The number of children who are so stigmatized is appreciable. They are found in both sexes and at every social level. Their chances of normal development and proper fulfilment are prejudiced and for this reason they present an important and challenging problem of child health. The handling of this problem is largely the responsibility of the family doctor and it calls for just those qualities of wisdom, common sense and tact that are his stock in trade.

THE CLINICAL PICTURE

In so much as the very essence of this condition is its indefiniteness and lack of precision there is no constant clinical picture to be drawn. One feature alone is almost constant and that is the parental attitude rather than any manifestation in the child himself. The parents of these children are invariably convinced of some organic defect in the child, and this conviction is accompanied by a sort of spurious pride in their own resulting devotion. Generally they will produce some rationalization of the etiology, which may range from hereditary causes through prenatal influence to some hypothetical present abnormality of growth, of nutrition or of endocrine function. Authority for this rationalization often derives from ill-digested, pseudo-scientific reading, but all too often it stems from injudicious solicitude on the part of an attending doctor.

The child himself may be overgrown or stunted, fat or thin, mercurial or phlegmatic, energetic or lackadaisical. When pressed for a specific complaint there will generally emerge from a lengthy catalogue one of two; either an unusual susceptibility to disease or a reduced capacity for physical activity. These complaints will nevertheless be vague and ill-documented, and the picture these children present is nothing if not indefinite. The essence of the problem of their management is first to reduce a vague unscientific jumble of notions to terms of simple pathological facts, and secondly, to get the parents to accept a regime based on these facts and to abandon their other preconceived ideas.

THE IMPORTANCE OF CORRECT DIAGNOSIS

It is one of the aphorisms of medicine that diagnosis should precede treatment. Perhaps in no type of case is this aphorism more important and more

often disregarded. The diagnostic field is almost unlimited. A great many of these cases have indeed to be undiagnosed and released from pseudo-therapeutic restrictions, but there is a small minority of them in which unsuspected chronic disease is in fact present and for which a progressive line of treatment may well prove disastrous. To exclude this possibility the first essential is a meticulous and comprehensive history and examination. Chronic rheumatism, chronic nephritis and, less commonly, diabetes mellitus, bovine tuberculosis, and congenital syphilis are some of the organic diseases that can creep most insidiously on the adolescent. This is by no means an exhaustive list of the conditions that may occasionally be revealed and have always to be excluded. Thorough examination will generally clear them out of the picture, to which indeed they do not properly belong. Diagnosis of a major organic disease takes the child by definition out of the group under consideration, and this is therefore not the place to discuss the management of these diseases, important though that may be.

RECURRENT CONDITIONS

Now let us turn to those children who suffer from recurrent types of disease and in whom an episodic disability is allowed to spread its influence over the whole of their lives. The allergic manifestations, asthma, eczema and migraine, are important examples. Epilepsy will find a place in the group. Although less well defined there is also the child "who catches everything that is going". This latter type is I think familiar as a recognizable clinical entity. Sometimes the susceptibility is due to some contributory organic condition such as nasopharyngeal lymphatic hypertrophy, chronic pneumonitis, achlorhydria, which renders some part of the body a *locus minoris resistentiæ* to infection. Often, however, children, without any such demonstrable lesion, appear to be unable to acquire a lasting or solid immunity to the common coccal or virus infections of the normal environment. Many children appear to go through such a phase, which is generally temporary. The susceptible years appear to be during the more active phase of puberty. Often the victims have spent their early childhood abroad or have been otherwise isolated from the immunizing effect of the common infections inseparable from an early childhood spent in the normal "sociable" environment of these Islands. In practice therefore they get these infections at a later age and concentrate their incidence into a shorter span.

Treatment.—We are not here concerned with the treatment of the acute disease episodes and the underlying contributory conditions that mark this group. It is rather our business to consider the management of these children during their free periods. There is a great temptation here to play for safety and, under the pressure of parental concern, to pile the Pelion of indiscriminating restriction on the Ossa of temporary natural disability. In some of these youngsters some restriction is inevitable but it should be imposed with a specific therapeutic end in view and never merely by rule of thumb. The aim in every case should be to let the child lead as nearly normal a life

as he can without ill-effects. The method of a "safe" base line with a controlled progression of graduated increments will yield surprising results in apparently most unpromising cases. Resistance to infection, freedom from allergic crises, even avoidance of epileptic seizures, all depend as much or more upon the maintenance of good general bodily functioning as upon specific measures. Exercise, fresh air and interesting occupation are at least as important for this purpose as rest, coddling and the boredom so prone to result from restraint in adolescence.

In much the same way a single major acute illness can become the foundation on which is built an unnecessary structure of semi-invalidism. During most acute illnesses all the organs of the body are affected, work below their full efficiency and require to be relieved of unessential demands. In almost all cases, however, these secondary effects are directly related to the toxæmia of the acute phase and pass off in a matter of a very few weeks after the subsidence of this phase. Persisting "weaknesses" of heart, lungs and other vital organs are much more often confessions of badly managed convalescence than statements of demonstrable pathological fact. The treatment of an acute illness should not cease until full health and function are regained. Medical rehabilitation should be an active and not a passive business. With intelligent supervision, full function, both physical and psychological, can often be regained rapidly, whereas without it there is a danger of the disabilities of the acute illness being prolonged indefinitely. If this important principle receives attention a considerable number of children will never get into the "delicate" state and others will be rapidly hoisted out of it.

THE QUESTION OF NUTRITION

In lay circles, at any rate, malnutrition is often blamed as a cause of chronic subnormal health in adolescence. Absolute malnutrition to any significant extent must be very rare in this country under present conditions of food distribution. The possibility of differential malnutrition is not, however, so negligible. Particularly should protein deficiency be looked for in the rapidly growing adolescent. The maintenance of an adequate protein intake depends under present rationing upon a generous use of milk and fish. The average child should get sufficient milk in the day to provide nearly half his optimum protein requirement. The main meat or fish meal should account for at least another third, and in most households this meal is of fish for something like half the week. Unfortunately milk and, to a greater extent, fish are foods which adolescents not infrequently dislike. If this dislike is allowed to result in the habitual exclusion of either of these foods from the diet, protein malnutrition may easily occur, and it may produce an anæmic, susceptible, ineffectual child who fits exactly into our group. In the absence of any other etiology this possibility should always be considered. I have seen several dramatic "cures" achieved by its recognition, and I believe it to be much more common than is generally suspected. It

is certainly commoner in my experience than the more fashionable vitamin deficiencies. They probably are to be found on occasion, but their effects on health are less general and far-reaching and I do not believe that a vitamin deficiency *per se* will ever bring a child into the particular category that we are discussing. Current rationing provides an adequate supply of all essential food factors but it leaves little margin. Its restrictions impose difficulties in maintaining palatability and variety, and it is the lack of these that results sometimes in the disappearance of those slender margins.

CARDIOVASCULAR AFFECTIONS

Circulatory invalidism in adolescence is an important subject about which clear thinking is particularly necessary. For practical purposes organic heart disease in adolescence is due to one of three conditions: congenital heart disease, juvenile rheumatism, or, more rarely, subacute bacterial endocarditis. All these conditions are susceptible to exact diagnosis and in the absence of such diagnosis the term "heart disease" should not be used. Many dramatic circulatory symptoms in childhood are due to faults in the peripheral circulation and not in the heart. One of the physiological miracles that we are most apt to take for granted is the power of the human body to maintain hydrostatic equilibrium in the circulation despite the most rapid and extreme changes in its physical environment. The neuromuscular mechanism that works this miracle must be so sensitive and complicated that it is only surprising that it falters relatively rarely. Sometimes it does fail to keep pace with the demands of rapid growth or gets rusty after the toxæmia and disuse of an acute illness, and there results effort intolerance, palpitations or even fainting attacks that are so often wrongly ascribed to a "tired", "strained", or "poisoned" heart.

This faulty labelling is the more to be deplored because it leads to wrong *treatment*. The most important therapeutic measure for a diseased heart is rest to reduce the load on a handicapped myocardium. In the case of peripheral circulatory inadequacy, on the other hand, it is a question, not of an organically damaged organ, but of a complex functional mechanism that has got temporarily out of gear. The requirement here is rehabilitation by means of use, and calls for controlled exercise rather than rest: exercise of the general musculature for the sake of the part this plays in the mechanical assistance of venous circulation, and specific exercise of the arterial musculature through the "vascular gymnastics" brought about by the varying physical conditions of an active outdoor life. Correct treatment of this type of invalidism depends therefore upon correct diagnosis, which is too often prejudiced by reliance on a single physical sign or symptom and a failure to take into consideration the complete clinical picture. Diagnosis is not always easy and it is in these cases particularly that the temptation to play safe is great. Let it be remembered that so-called safety may involve condemning a healthy child to a prolonged period of unnecessary invalidism.

PSYCHOSOMATIC CONDITIONS

It is not necessary to go all the way with the psychoanalysts to accept the existence of psychosomatic disease and to believe that it is often based on some subconscious wish fulfilment. The parent-child relationship is one that is highly charged emotionally and for that reason one that is prone to frustrations and distortions. These may take the form of a subconscious desire on one or both sides for a prolongation of infantile dependency, and to forward this desire symptoms of physical inadequacy may well be produced. An etiology of this sort must be in our minds when we are faced by the problem of a delicate adolescent that appears inexplicable on purely physical grounds. Often the recognition of the causation and an approach on common-sense lines will cure the symptoms without resort to the more esoteric forms of psychotherapy.

CONCLUSION

I have indicated a number of the more common types of pathological process that may produce the type of disability under discussion. In the management of these and other similar conditions it seems to me that there is one fundamental principle that is common to all. Adolescence is a time of expansion, of physical growth and of mental and emotional experiment. The vital stream comes pouring out of the narrow channel of childhood and surges through the rapids that lead to the broader reaches of adult physical and psychological adjustment. Therapeutic endeavour should harness the impetus of this stream and should rarely attempt to dam it back. A repressive approach is contrary to the natural pattern of this time of life and should be resorted to only under the most unequivocal indications. Rest and restriction, it is true, have a part to play in the treatment of many of the conditions that we have considered. That part should be in support and not in replacement of exercise and licence. We should secure an adequacy of rest rather than fear an excess of exercise; increase the former more readily than curtail the latter. Restriction should be employed to focus endeavour and not towards the production of a dangerous vacuum. At no other time of life are there such funds of natural energy to be used in the cultivation of health. Nature is on our side to an extent that she never is before or after this period.

Physical standards in adolescence vary over a wide range and it cannot be claimed that there is not a certain small residue of the constitutionally substandard. It is, however, possible to state with confidence that many individuals are wrongly placed in this category and are the victims of well-meaning but none the less dangerous mismanagement. As doctors it is given to us rarely to cure disease. It is therefore the more important to avoid any hand in the production of ill-health. The delicate adolescent is rarely the neglected adolescent. He is all too often crippled by the indiscriminating concern of loving parents which sways with its momentum the confidence and the judgment of the unwary physician.

THE ENDOCRINES IN ADOLESCENCE

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THE endocrine changes that influence the years following puberty begin to act some time before its onset. For the purpose of this article therefore, adolescence will be defined as that period, spreading over several years, during which sexual maturity develops in both boys and girls. It encompasses the menarche or onset of menstrual bleeding that may occur without ovulation, and puberty when reproduction first becomes possible.

The central and all-important event that largely determines the physical and mental changes of adolescence is the increased activity of the anterior lobe of the pituitary gland. The great rise in secretion of the pituitary gonadotrophins, with a secondary outpouring of gonadal hormones, shows itself in a clear-cut manner in girls by the onset of menstruation. The influence of these increased secretions may, however, be seen to extend over several years in both sexes, manifest by familiar bodily changes, such as prepubertal enlargement of the breasts in girls, an increase in size of the testicles in relation to the epididymis in boys, and the appearance of pigmented pubic and axillary hair in both sexes. The body weight and height both increase rapidly during the months that embrace the onset of puberty, and the hip measurement taken at the greater trochanter also shows marked increase at this time (Ellis, 1948).

The urine of children, which from the age of three contains small amounts of ketosteroids and œstrogens, shows them in a considerably increased amount round about the tenth year and, at the same time, the follicular stimulating hormone, a pituitary gonadotrophin, has been detected in the urine of girls. The endocrine influences that accompany increased pituitary activity therefore exert themselves over several years and should reach a peak round about the age of twelve to fourteen with the onset of puberty, and thus the endocrine problems that may confront the practitioner in the adolescent are chiefly related to abnormalities in this event. Among these problems the extent of normal variations, both in physical characteristics and in the time of their appearance, is always presenting itself.

EARLY ONSET OF ADOLESCENCE WITH PREMATURE PUBERTY

Premature puberty in girls.—It is difficult to give a definite age before which a girl who menstruates can be regarded as suffering from precocious puberty. Selye (1947) states that when puberty occurs before the ninth birthday, it should be considered to be premature, and this seems a practical, albeit

arbitrary, working rule. It is well known, of course, that children who have subsequently grown into normal, although rather short, women, have reached puberty years before this, the earliest recorded case being at 7½ months, but it is reasonable to suggest that girls who menstruate before their ninth birthday should be thoroughly investigated. This will prove negative in the majority of cases, but occasionally a granulosa-celled tumour of the ovary, an adrenal cortical tumour, or a tumour or encephalitic change in the region of the hypothalamus will be found. The investigator must bear these conditions in mind, and should insist on an accurate estimation of the urinary oestrogens and 17-ketosteroids, in addition to clinical and radiological examinations. If any of the results are of doubtful significance it is justifiable to perform a laparotomy.

One important difference between the far more common constitutional group and the pathological group must be stressed. It is that the constitutional cases have a true puberty with ovulation and are particularly liable to become pregnant, as their minds do not mature as rapidly as their bodies. Their period of adolescence is therefore prolonged and especially difficult, and the wisdom and understanding of the practitioner in advising their parents are the fundamental factors in their management.

Premature puberty in boys.—Precocity in boys is also constitutional in most cases and is sometimes termed macrogenitosomia præcox. It tends, as in girls, to run in certain families and races and is then genetically determined. That genetic influences are not always the cause of unexplained cases is shown by a boy who at the age of seven had marked macrogenitosomia for which no pathological cause was found, although his twin brother was a perfectly normal child for his age (Gardiner-Hill and Richardson, 1939). Adrenal cortical tumours, cerebral lesions in the hypothalamic region, among which pineal tumours, although they have no intrinsic endocrine function, feature prominently in the literature, and testicular tumours, all have been reported as resulting in precocity in boys. These cases therefore require just as careful consideration as do those in girls, and the main problem in the management of the constitutional case is once again wise guidance throughout the adolescent years.

DISORDERS OF ADOLESCENCE ASSOCIATED WITH THE ONSET OF PUBERTY

Disorders of puberty in girls.—The onset of puberty should be followed by the rapid establishment of a normal menstrual rhythm, but not infrequently irregular, excessive, or painful menstruation occurs. The underlying cause may be developmental, but many cases are due to a failure of the anterior lobe of the pituitary gland to excrete gonadotrophins in proper amounts or of the ovary to react to them. Discussion of these disorders is beyond the scope of this article and reference to them should be made to books on gynaecological endocrinology (Bishop, 1946).

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these cases eventually menstruate spontaneously, but if the delay is prolonged after their seventeenth birthday, Bishop (1946) advises the production of a series of œstrin withdrawal bleedings, as these may be followed by true menstruation. The more severe degrees of ovarian deficiency rarely respond with true menstruation to treatment with œstrogens.

Severe defect in ovarian function, ovarian agenesis, has been described as a syndrome by Turner (1938). These patients with primary amenorrhœa are abnormally short, under five feet in height, with ununited epiphyses, osteoporosis, no true breast development, and scanty or absent body hair. Other features that characterize them are webbed necks and wide carrying angles due to congenital bony deformities, and a high incidence of hypertension, some cases of which are due to coarctation of the aorta. Their urine contains an excess of follicular stimulating hormone, the reverse of the finding in pituitary dwarfism, and the absence of ovarian tissue can be confirmed by peritoneoscopy or laparotomy. Substitution therapy with œstrogens may produce the appearance of maturity but does not lead to true menstruation.

Lack of uterine response to normal endocrine stimulation.—Delayed puberty may result from a failure of the uterus to react to normal endocrine influences. Here the secondary sex characteristics are normal but the uterus is small and ill-developed and œstrogens rarely lead to the establishment of regular menstrual cycles.

Delayed puberty may herald normal menstruation, but the late onset is often followed by long periods of amenorrhœa or oligomenorrhœa, accompanied by acrocyanosis and evidence of an over-secretion of androgens, with hypertrichosis and acne. These disfiguring results of an imbalance between ovarian and adrenocortical hormones are real disabilities to young girls and add to the psychological stresses almost always attendant on puberty.

DISORDERS OF THE BREASTS IN GIRLS

Growth of the breasts occurring round about puberty is due to the action of œstrogens. This may be excessive as a result of over-secretion, or from over-sensitivity of the breast tissues themselves, with the development of macromastia, or it may be inadequate with consequent small ill-formed nipples, areolar and glandular tissue.

There is no endocrine treatment for macromastia, which must be controlled by local supports or, in gross cases, by plastic operations done by a surgeon with special experience. Under-developed breasts sometimes enlarge when œstrogens are given by mouth or by inunction, but often the tissues are so insensitive that they fail to respond to even very large doses. Excessive œstrogen action is thought by some to lead to the painful and pre-occupying condition of lumpy breasts or fibro-adenosis. Androgens relieve these patients but, as they have masculinizing effects, minor and temporary though they may be, they are best avoided in the adolescent. This is especially so as any treatment with a highly suggestive value may give equal

DELAYED PUBERTY IN GIRLS

The onset of true menstruation may be delayed until the twenty-first year and yet become regular and be followed by normal pregnancies. Nevertheless, it is generally agreed that if menstruation has not begun by the seventeenth birthday, the case should be regarded as one of delayed puberty and investigation begun with a view to attempting treatment. The fault may not be in the endocrine glands at all, but be due to some general disease, social factors or developmental abnormalities that should be excluded straight away by general investigation and a gynaecological examination under an anaesthetic. If an endocrine disorder is believed to exist, the defect may lie at the level of the pituitary, the ovaries or the uterus.

Lack of pituitary function.—A minor degree of hypopituitarism may lead to delayed puberty and primary amenorrhœa with the late appearance of secondary sex characteristics and development of the breasts. The girls are often obese with round rosy faces, small mouths, good teeth and fine skin. They rarely require any active treatment beyond a reducing diet, as the consequent loss of weight is not infrequently accompanied by the appearance of puberty.

When a more severe lesion of the pituitary is responsible for delayed puberty it is part of a pituitary infantilism. These children are abnormally short with infantile proportions, but ununited epiphyses. They are usually well nourished or even fat, but may show some wasting and premature senility if the pan-hypopituitarism is sufficiently severe. Their secondary sex characteristics are absent or minimal and their soft childish bodies have fine hairless skin. Intellectually they are often above the average, but emotionally they are immature and at times difficult to handle. The chief diagnostic points are their childish appearance with a shorter measurement from the pubis to the soles of the feet than from the pubis to the vertex, and very small amounts of follicular stimulating hormone in their urine. The primary lesion may be either hereditary pituitary dwarfism or else a destructive or inflammatory lesion of the anterior lobe of the pituitary, usually a craniopharyngeal duct tumour, and therefore evidence of an expanding intracranial mass must be sought.

Endocrine treatment, which should aim at replacing all the trophic hormones, the lack of which goes to make up the clinical picture, is severely limited because so few active preparations are available. We still await a growth hormone for general use in clinical medicine, and adrenocorticotrophin is only obtainable for experimental work. For practical purposes treatment amounts to the administration of serum and chorionic gonadotrophins in high dosage, dried thyroid extract and, if the gonadotrophins fail, œstrogens. This treatment is not infrequently followed by some increase in the rate of growth, but true menstruation results only rarely.

Lack of ovarian function.—Minor degrees of inadequacy of ovarian function are commonly seen when primary amenorrhœa is associated with poor breast development, seborrhœic skin and cyanosed extremities. Most of

mammary tissue at some time, including an increase in the height of the nipples. These changes are due to the action of œstrogenic substances which, as is well known, occur in males. True *gynæcomastia* is an advanced stage of this proliferation of glandular and areola tissue and is relatively rare. It may result from trauma to the testis, a malignant growth such as a teratoma, and has been reported in such varied conditions as adrenal cortical tumours, hypernephromas, and thyrotoxicosis. It is also seen to a marked degree in boys receiving œstrogens for acne and, in part, counteracts the benefit to the boys' morale that may have resulted from an improvement in the disfiguring skin condition. Gynæcomastia is the main feature in a condition in which the interstitial cells of the testicles produce normal amounts of testosterone and are hypertrophied, but there is tubular atrophy with lack of spermatogenesis and an excess of follicular stimulating hormone in the urine (Klinefelter *et al.*, 1942). The secondary sex characteristics may be normal or over-developed, and persistent and disturbing erections sometimes occur (Richardson, 1946). The condition can be diagnosed with certainty by the simple procedure of testicular biopsy.

No form of endocrine therapy has as yet been found for gynæcomastia and a plastic operation is the only cure. Before it is undertaken it is clearly a duty to exclude those conditions in which it is only a symptom and to try to assess the effect of the deformity on the boy. Some are so deeply distressed by it that something radical has to be done for them, whereas others pass through school life and early manhood without any apparent concern.

OBESITY IN THE ADOLESCENT

Obesity in adolescence is commonly associated with delayed puberty in either sex. Endocrine abnormalities are often postulated to explain these cases but they are rarely demonstrated and the cause of the obesity is nearly always over-eating by the child, encouraged by the solicitude of the parents. A fat child with some delay in puberty is often regarded as suffering from a pituitary lesion or, more specifically, that rare and serious condition, *dystrophia adiposogenitalis* (Fröhlich's syndrome), whereas in fact he simply over-eats and under-exercises. Colour is lent to the belief that these cases belong to a special pathological group, by their resemblance to each other, due to their healthy round and rosy faces, shapeless immature bodies and delayed puberty. The real common factors are large appetites, a marked preference for carbohydrate foods, and mothers whose fixed belief it is that the child hardly eats enough to maintain his strength. If it is possible to obtain good cooperation from the patient and mother over the diet, the child as he loses weight will, in most cases, undergo the changes of puberty in the normal way. Obesity and menstrual disorders occur in some endocrine diseases that are incidental in the adolescent, such as hypogonadism, Cushing's syndrome, some pituitary or hypothalamic tumours, and certain instances of the adrenogenital syndrome, but their number is small.

symptomatic relief. It must always be remembered in this connexion that the emotional accompaniment of any abnormality of the breasts is very great, and apparently trivial variations from the normal may have enormous symbolic significance to the patient, and require skilful reassurance in dealing with them.

DELAYED PUBERTY IN BOYS

Delayed puberty in boys as well as in girls may be a familial characteristic and of no pathological significance. It may, on the other hand, result from a pituitary disorder or from a primary gonadal failure. The clinical picture and principles of treatment of the pituitary cases are the same as those already described for girls, and need not be discussed further.

Testicular failure in boys may lead to eunuchoidism, a condition that resembles eunuchism clinically, but is not the result of castration and is produced by either disease of the testicles or by a congenital testicular hypoplasia. The boys are usually tall and have abnormally long limbs and arm span in relation to the length of their bodies. They have unbroken voices, soft hairless skins and feminine contours, but no true gynæcomastia. The external genitalia are small as are their testicles, which have usually descended into a poorly pigmented scrotum. The chief points that distinguish eunuchoidism from pituitary infantilism are a lower measurement that is longer than the upper and the relatively large amounts of follicular stimulating hormone in the urine. The epiphyses are widely open in both conditions. Substitution therapy with testosterone is an effective measure, and in most cases will result in some growth of the penis, scrotum and body hair, a drop in the voice, the appearance of erections, and an increase in general muscular development. Most important of all is the more mature, confident and positive approach to life that is obvious to the patient and to his companions.

Undescended testicles.—There is usually no evidence of any androgen deficiency in boys with bilateral undescended testicles, but a certain number are on record who had delayed puberty (Bishop, 1945). The importance of bringing the testicles to the scrotum before the age of twelve lies, not in the fear that the interstitial cells may fail to produce enough androgens, but in the possibility of impairment of spermatogenesis if they are left too long in the wrong environment. When no mechanical obstruction exists, chorionic gonadotrophin is of real value in assisting descent by increasing the size of the testicle and lengthening the structures of the cord. It should be given a trial round about the age of ten, but if the testicles are still out of the scrotum by the age of twelve, operation should not be delayed.

BREAST CHANGES IN BOYS

Breast changes, sometimes known as adolescent mastitis, are common in boys about the age of puberty. Jung and Shafton (1935) examined the height of the nipple and the size of the areola in 169 boys between the ages of twelve and seventeen, and found that 70 per cent. had enlargement of

THE ADOLESCENT AT WORK

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ADOLESCENCE reminds us of pimply boys and giggling girls, of the period when our youngsters lose the pleasing naïvety of the uninhibited child, but have not yet acquired the veneer of the young adult. Authority no longer goes unchallenged and there is an awakening of new powers. As parents and doctors we are familiar with these changes and the difficulties they hold for the youngsters and for us. It is doubtful, however, whether we think of one of the most important changes that takes place at this stage; not a change of adolescence itself, but a social change from school to work. Many doctors know little of factory life and what it means, although they are probably familiar with the heavy-eyed bell-hop who runs their errands late in the evening at a restaurant, or perhaps they are more familiar with the early rising newspaper boy; but few know much of the changes imposed on the majority of children when at the age of fifteen they begin work.

To most adolescents in Britain the change from school to work is the greatest they ever experience. One week the adolescent is a care-free schoolchild, learning under the kindly eye of a teacher; the next week he is a number that clocks in at the factory gate, works in a gang with his own eye on the boss, and scurries off home when the whistle blows.

After ten years of regular schooling, with its 27-hour week and 12 weeks' holiday in a year, they begin a 44-hour week with one or two weeks' holiday a year. They get out of bed more than an hour earlier, perhaps have farther to travel, work harder under their first boss and eventually return home later than usual. If absent from school the Attendance Officer would have called at their home to shorten the break in their training, but the day after their fifteenth birthday no official worries them if they stay away from work, or if their training lapses, or even if they are unemployed—as often occurred before the war. But pay day brings a wage packet, and more spending money. Now on their own earnings they can go to the cinema, buy cigarettes or take the girl friend out to a dance; they feel grown up, they are a number on a factory roll, they have arrived. All this happens not gradually, but overnight.

Such an abrupt transition would be a strain at any age. Even for adolescents Fleming (1948) shows that the stress is not so much biological as social, occurring at the time the youth is struggling to reach maturity in the strange new adult world. Anthropological studies by Mead (1935) in Samoa and New Guinea, and Elwin (1948) in aboriginal Indians, reveal few problems during adolescence among these primitive cultures. Gorer (1949) states that "the social and legal raising of the nubile age in Western society is a comparatively recent phenomenon and would seem to be connected with the increasingly complex technology of our civilization,

THE THYROID GLAND IN ADOLESCENCE

A *puberty goitre* is due to a deficiency of iodine that may be relative and part of the increased physiological stress of puberty, and which may normally lead to some enlargement of the thyroid. These goitres are colloid and not toxic, and their chief harmful effect is probably psychological, due to anxiety over their significance or their appearance.

Toxic goitres occurring in adolescence, as at other ages, are far more common in females than in males. They may have no special features but some adolescent girls, although showing, to a marked degree, florid signs of thyrotoxicosis seem to lose little weight or even to increase, and to be far less ill than would be expected for a comparable rise in metabolism in a more mature woman. They often respond to Lugol's iodine and rest, with a remission that may amount to cure, and constitute one of the groups of thyrotoxic cases for which thyroidectomy was often unnecessary even before the advent of anti-thyroid substances in clinical medicine. Some such temporary thyrotoxicosis of minor degree may account for complaints of tiredness, menstrual irregularity, and irritability in certain adolescent girls.

Hypothyroidism in the adolescent is an important condition as, when it is the cause of stunted growth and delayed puberty, simple substitution therapy, if given early, is highly effective. It is easily overlooked and should be considered in all cases, but in particular when constipation is a prominent symptom.

CONCLUSIONS

This brief survey of the endocrines in adolescence has omitted much, including mention of many important conditions that may occur during the years under consideration: Addison's disease, the adrenogenital syndrome, Simmonds's disease, diabetes mellitus, to name but a few, are serious omissions, but they are deliberate ones. It is felt that the main endocrine problems of adolescence are the disorders of growth and sexual development that disturb progress towards maturity. They disrupt this difficult decade, and have a profound psychological as well as physical effect. It is hoped that by concentrating on those aspects of adolescent endocrine disorders that are near to the range of physiological variation, a better impression may be gained of the true influence of the endocrines on that normal, but so highly variable, individual, the adolescent.

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youngsters—errand boys and cinema usherettes, for instance, may work until 10 p.m. Further, the juvenile working in a factory has the advantage of medical supervision, both on starting work and at yearly intervals. There is no such statutory medical examination for any other group of adolescents. It is understood that the National Coal Board is now making arrangements for the initial examination of boys entering their employment, although there is no statutory requirement to this effect, nor is there any regular re-examination. The importance of medical advice as to types of work for all school-leavers is apparent.

It is at present promised that from April 1, 1950, certain young people will be required to spend one day each week, in working time, at a Continuation School or County College. Here they are to be taught general subjects: science, current affairs, English in its modern media of the cinema, radio and television. If the school-leaving age is raised in the future to sixteen, only the older adolescent will work—and then only for forty hours a week. Since 1930 the leading American states have kept adolescents at Junior High School until sixteen years of age, continuing a broad education, and since 1936 no girl under 18 years could work in a factory doing government contracts. Educationalists feel that juveniles should continue full-time school for as long as they can learn academically. This policy would carry them through a biological adolescence at school with teaching on a wider basis aimed at preparing them to take their place easily among adults.

JOBS FOR JUVENILES

Each year sees some 600,000 boys and girls reach adolescence. In 1947 the percentages of each age-group insured for work were: 14 to 15 years, 55 per cent.; 16 to 17 years, 75 per cent., and the National Service reduced this for 18 to 20 years to 35 per cent. Before the war 13 per cent. continued at Secondary School, but this has now increased to 15 per cent., although under 3 per cent. proceed to University in contrast to 10 per cent. in some New England states.

As shown in figure 2 (p. 291), half of the new boys entering industry at the age of fifteen select engineering, metal goods, wood-working, cars and aircraft—certainly a young boy's dream. Building and contracting absorb 13 per cent. to serve their time as painters, plumbers or bricklayers. Farmers' sons are often not insured, but 6 per cent. of school leavers begin work on the land, whilst the same numbers enter offices when aged fifteen—although an increased proportion (one-fifth) of secondary school leavers aged sixteen to eighteen become clerks. However, 17 per cent. of boys and 30 per cent. of girls at the age of fifteen begin their training towards adult work and happiness by entering retail distributive trades as shop assistants, or as errand boys for the butcher, the baker or the grocer. About equal rates of 3 per cent. drift into hotels as bell-hops and kitchen porters, or take a

which demands post-adolescent education, and consequently the postponement of social maturity". Thus the aggressive moods of some problem children may be healthy and virile reactions of human nature trying to adjust itself to our present society.

LEGAL SAFEGUARDS ON WORK

What has been done in Britain to ease the strain on the adolescent of this transition? So far our law-makers have been concerned with physical safeguards. A glance at figure 1 shows what has been done over the last 150 years in two directions—the minimum age at which a youngster may enter a factory and the weekly hours he may work there. Legal restrictions on the age of children working in textile factories were first made in 1819, when those below nine years of age were excluded. It was not until 1842 that boys under ten were excluded from the pits. In 1887 the age permitted for work underground was raised to twelve, and in 1911 it was again raised to fourteen years. As recently as 1936, however, there were 70,000 boys under sixteen years of age working below ground.

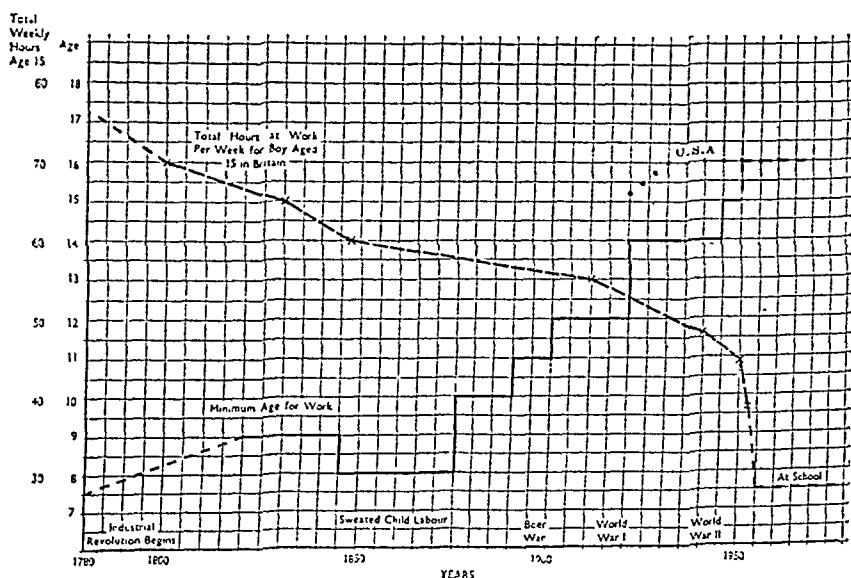


FIG. 1.—This chart shows the changes in minimum age and maximum daily hours of work imposed by Factory Legislation in Great Britain over the last 150 years.

At the present time the *health supervision* of the adolescent varies enormously. If he works in a factory and is under eighteen years of age he may not start work before 7 a.m. nor may he work after 8 p.m., and not more than forty-eight hours in a week. If he is under sixteen he may only work between 7 a.m. and 6 p.m. and may not work more than forty-four hours in the week. Such restrictions on hours do not apply to many other

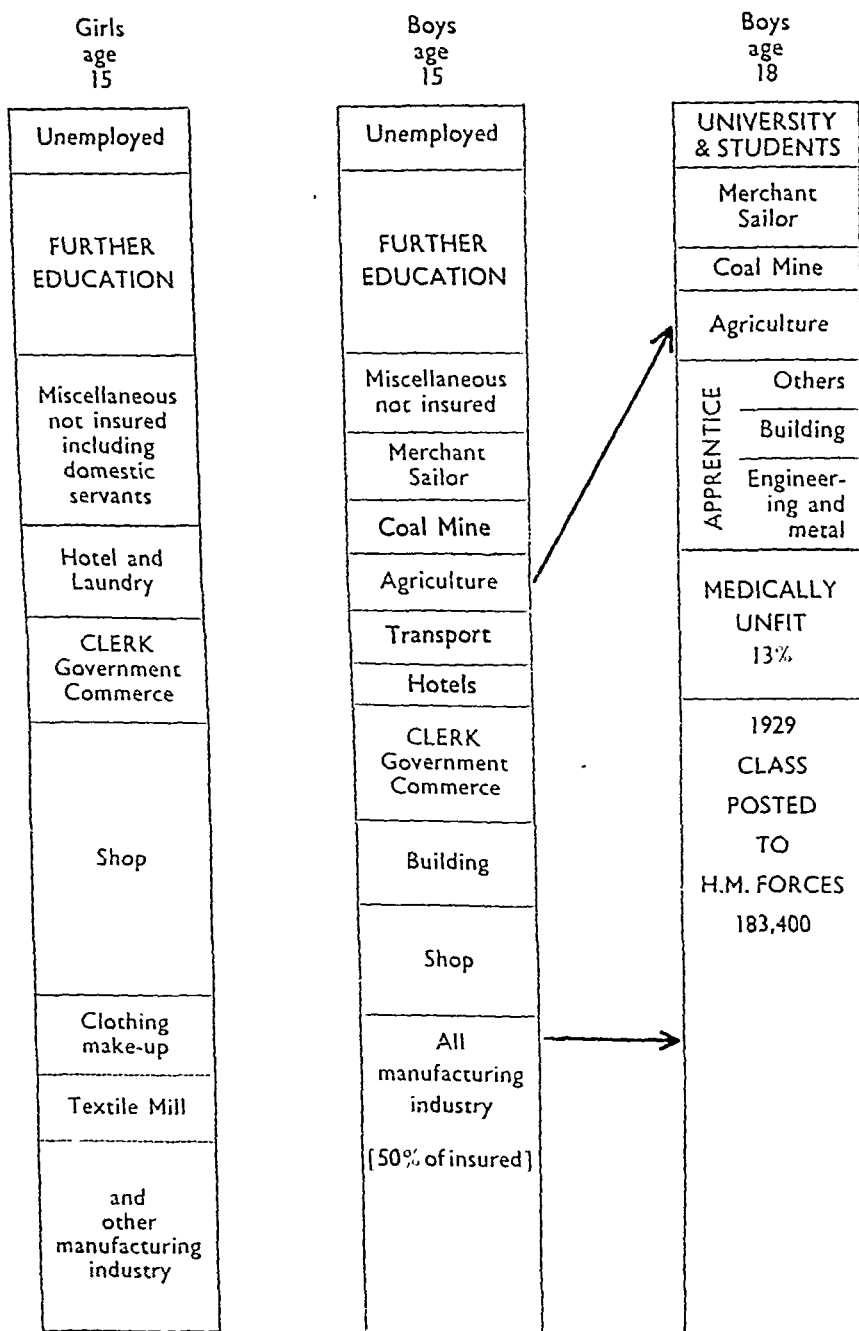


FIG. 2.—Occupations of Juveniles in Great Britain 1946-47. Diagram compiled to show the distribution of juveniles in various occupations (from *Ministry of Labour Gazette*, November 1947 and December 1948).

man's size job in pit or quarry, or let their eager wanderlust lead them to the sea.

Engineering and metal working also attract the girls, but more by good wages and conditions than the craft; with the food industry they absorb 30 per cent. of girls leaving school at the age of fifteen. Textile mills take 8 per cent. but have vacancies for as many more again. The making up of clothing uses 15 per cent. More girls than boys enter offices and 35 per cent. of girls leaving secondary school at the age of sixteen to eighteen become typists. It is difficult to estimate the numbers of domestic servants; 5 per cent. become insured in hotels, laundries and personal services, but probably 10 per cent. do some part-time work in homes.

THE WORK OF THE APPOINTED FACTORY DOCTOR

It has been pointed out that each year approximately a quarter of a million youngsters on leaving school enter a factory and for this reason are better protected than others: not merely are their hours of work controlled but also their working conditions; the law recognizes that they are likely to be clumsy and awkward and forbids their working on dangerous machines or with certain dangerous substances; yet until 1947 the accident rate for boys was always higher than for men. These young people also have some statutory medical supervision. For over a hundred years the service of doctors has been required in connexion with the young entrant to our factories. For many years, however, the terms of the certificate required of them were negative and the Certifying Factory Surgeon gave his opinion that the child was "not incapacitated by disease or bodily infirmity". In 1924 a Departmental Committee (Medical Examination) reviewed the subject and made many sound recommendations concerning the medical examination of juveniles. Slowly, many of these recommendations have been adopted, and in 1937 the nature of the examination was improved. At this time also the Certifying Factory Surgeon changed his name to that of Examining Surgeon. As such he had power to reject a youngster as unfit for work.

In 1946, out of 260,000 examinations, the reasons for rejection were, in round numbers: 2000, *pediculosis capitis*; 500, defective vision; 300, skin trouble; 200, heart disease, and 100, lung defects. It is strange that halfway through this hygienic twentieth century, with full employment, stable wages, adequate food, soap and water, and a school medical service, that the head louse should cause over two-thirds of the medical rejections for work, particularly when two applications of an appropriate hair cream would solve the problem.

Under the 1948 Factories Act the Examining Surgeon's name has again been changed, he is now called the Appointed Factory Doctor, and medical examination of juveniles entering a factory is to be followed by an annual re-examination until the youth reaches the age of eighteen (the International Labour Office recommended the age of twenty-one). The 1924 Committee had recommended that doctors carrying out these examinations should

years later. For the vast majority of juveniles entering industry the appointed factory doctor is their only regular medical supervisor and, although the statutory regulations are minimal, there is great scope for the doctor doing this work, provided he works in the closest collaboration with the manager or his representative. The appointed factory doctor can give to the small unit the same type of help that the Industrial Medical Officer gives to the large firm. It is true he may find a less receptive Management, but this is by no means always the case, since many employers have a great sense of responsibility for their young employees and are anxious for any help the doctor can give them.

THE INDUSTRIAL MEDICAL OFFICER

The industrial medical officer has a greater opportunity in this sphere than the appointed factory doctor. His position gives him more scope to study the transition of adolescents and to help them to maturity of body and mind and to the full society of the workshop. His duties, which include a close medical supervision of the juveniles, are largely those of an educator, and it cannot be too often stressed that he is one of a team.

From a routine twice-yearly weighing of juveniles and interview by the trained industrial nurse, any sustained loss of weight will be detected. The doctor will not need to be reminded that the greatest cause of serious illness and death among adolescents is *pulmonary tuberculosis*. The Prophit Survey (1948) drew attention to the Irish immigrants and the juveniles from rural Britain as being particularly susceptible to attack when working in cities. Increased attendance at the ambulance room for coughs and colds or indigestion may conceal the insidious onset. Headaches, insomnia or dysmenorrhœa may be caused by low morale as well as by overwork. Fatigue can be prevented. Advice may be given to reduce cinema and dancing from five nights per week to two. As well as the usual breaks for national milk-cocoa or tea and a bun in the morning and afternoon, the works doctor may arrange a week's holiday by the sea, in "rest break" hostels, for overworked juveniles.

Prescription of suitable physical education can remedy *postural defects*. Juveniles in industry are prohibited from lifting heavy weights, but they can be taught good weight-lifting techniques in the fun of the gymnasium. Games should be encouraged, for if boys kick a football in the yard they are less likely to skylark into accidents on the job, and if typists snatch a game of tennis, basketball or hockey they may be less worried by headaches, expanding hips, and missed commas.

Adolescents can be encouraged to use the canteen if it notes their patronage of city milk bars. They will nearly always eat fish and chips and ice cream, and the doctor at first may have to dissuade a trained dietitian from over-emphasizing the neglected winter salads. Prices must be low, and this is often secured by a subsidy from the employer.

come under the control of the Local Authority. This recommendation has not been accepted and the lack of a sound link between the appointed factory doctor and the other local health authorities presents difficulties. Efforts have been made to overcome this, and the appointed factory doctor may make a special request to see the school health record. It is unfortunate that more routine use is not made of this school medical record. If it is worth making it is worth using, and the facts collected by the school medical officer should surely accompany the child across the departmental gulf separating school and work. In planning a comprehensive occupational health service it is essential to remember that one-half of our adolescents do not even have the benefit of this medical care.

So far as the details of a routine medical examination of an adolescent are concerned, little can be added to Bashford's (1944) excellent account:

"Though the height at this age may vary from 4'-9" to 6'-0" and the weight from 5 to 11½ stones, now that follow-up examinations are compulsory it is essential they are recorded. Examination of the physical condition would include the limbs and exclusion of herniæ and undescended testicle. Posture and feet would receive special attention, while the heart, lungs and urine must be examined—as well as ears, eyes and teeth. Where treatment is needed this must be arranged through the patient's private doctor and in a few instances it may be necessary to withhold permission to start work until this has been completed, to ensure that the patient does not neglect it".

For those who are rejected as unfit for factory work on account of some permanent disability, there is now provision under the 1944 Disabled Persons (Employment) Act for these handicapped youngsters over sixteen years of age to be sent to training centres to learn trades compatible with their capacity. In this group the doctor has an important contribution to make to the vocational guidance given to the young person. However, it is unknown how many of the rejected juveniles take advantage of this scheme. As in the past, many probably drift to jobs outside factories where they need not pass the doctor. Such outside jobs are usually unskilled, such as errand boys, messengers or barrow boys, so that when the youngster with mitral stenosis reaches an age at which his exercise tolerance fails he has no skill for a sedentary job and is too old to train, and he often becomes unemployed.

To secure the full value of the annual re-examination by the appointed factory doctor the cooperation of the management will be necessary. Records of sickness absence and labour turnover should, for instance, be available to him, since these may draw attention not only to physical disease but to psychological maladjustment. The job, the juvenile or the foreman may each be a misfit. It is often at this stage that bad work habits begin. Lack of interest may lead to drifting from job to job or to sick absence which is nothing more than a symptom of low morale. This is a critical stage in the training of a young person, and the doctor and the employer together have opportunities for valuable preventive work which may bear fruit

and spermatozoa. They will listen to eugenics, evolution and economics; they want to sort out the disparity between their own life and that of Hollywood and the novelette. Coitus is on the same spiritual plane as partnership in a joint account in the savings bank. Jephcott (1945) finds that modern girls look on their jobs as only a pastime until marriage. It is a temporary source of income for their parents and extra pocket money for cinema, dancing, cigarettes and cosmetics. Work also provides a necessary contact with the new adult world as well as another arena, like the dance hall, in which to see and be seen by boys. The boys react very similarly to the girls, with the one exception that they realize that only sickness or unemployment can stop them having to work. They take more interest in training schemes and in their future in industry.

Industry is now recognizing its social function and is more ready to accept its responsibilities. To-day, with the raising of the school-leaving age, the decline in the birth rate and with full employment, there is a strange change in the juvenile labour market—many jobs and few young people to fill them. In Lancashire, for instance, there are twenty vacancies for every unemployed boy or girl. For purely economic reasons less enlightened industry is being forced to pay attention to these changes. It may well be that the law of supply and demand will do most to improve conditions for the juvenile in industry. The raising of wages and the need to economize in juvenile labour may well lead to its better use and give further opportunities to the doctor and personnel manager in their struggle for more satisfying work for the adolescent. Morgan (1943) showed that after ten years' training in school at national expense, 30 per cent. of boys and girls entered dead-end jobs which they left when aged eighteen without having added to their training or earning capacity, except for the development of muscle for manual labour. However, Jewkes and Jewkes (1938) in a survey of two thousand Lancashire adolescents, found that only one-half remained in the same factory after two years, and one-fifth tried three or more jobs in this time. This is only to be expected from their methods of choosing jobs. Some 40 per cent. apply at the factory gate, 30 per cent. use the influence of parents or friends, and only 20 per cent. use the facilities available at the Youth Employment Service bureau, where they could be assessed for ability and aptitude and then placed in a selected job.

YOUTH CLUBS WITHIN THE FACTORY

It is a characteristic of adolescence that boys and girls wish to mix informally, to make and break contact, to experiment in human relations—thus their high labour turnover. During the factory lunch hour they will hang around the canteen or in quiet backwaters talking juvenile shop, which is only subdued when adults come within earshot. To help them grow up it is an advantage for the juveniles to have, in the factory, their own club run by themselves. They will elect their own committee, forbid entrance to

Sickness absenteeism.—Sickness in adolescents is difficult to measure. Some works doctors feel that juvenile morbidity is increasing. Roberts (1948) compared the Post Office rates for the past fifty years. He records adolescent rates always lower than the adult, but with the well-recognized jump in both since the war.

ANNUAL DAYS SICKNESS ABSENCE AMONG POST OFFICE WORKERS

	Boy Messengers	Girl Probationers	All Men	All Women
1938	6.8	7.1	7.6	9.3
1946	12.4	14.2	12.3	15.9

Roberts is of opinion that the greater rate of increase among juveniles may be due to a poorer quality of entrant caused by the present shortage of juvenile labour.

The doctor can fulfil his rôle of educator in helping young persons to grow towards mental maturity. These "teen-agers" are alert, vivacious, curious and keen to learn about life. As any youth leader knows, they look to adults—preferably under the age of thirty-five—to discuss their newly discovered problems of life. They tend to regard severe school teachers and "starchy" nurses as a unique and impersonal neuter sex. They will "open up" to a doctor or sympathetic nurse who does not begin "When I was your age . . .". It must be remembered that the oldest of the 1949 vintage of sparkling adolescence was born in 1931, was just beginning school at the time of Munich, was ten (and perhaps evacuated from home) during the Battle of Britain, and had just left school when the war ended. War-time life is "normal" to them. Education for life must be in the adolescent idiom. The girls are experimenting through the whole range of cosmetics, adding oily vanishing creams to an already acned face. Tight elastic is used to "support" an undeveloped abdominal musculature, or pushes into the New Look territory fat from excessive "cream buns". The doctor by explanation, reassurance and advice on clothes and brassière can help the shy girl who is rounding her shoulders to conceal her developing breasts. They welcome health education on how Marlene Dietrich, although a grandmother, is still so photogenic, without the dowdy middle-aged spread of the adolescent's own mother.

These girls are anxious to discuss with doctors their changing human relations with boys and with adults. They want to understand courtship, marriage and conception. Almost one-half of primiparæ in England and Wales in 1945 were under twenty-four years of age. Of these first babies, one-quarter were born within eight months of marriage and this number equalled the illegitimate births for the same age-group—thus these adolescents require more than coloured diagrams of pelvic organs, amœbæ

Employment Officers from the Ministries of Labour and Education help him with advice. If he is medically handicapped in any way he is trained for a suitable job in open industry or in a sheltered workshop. As Sir Francis Fraser (1949) states: "doctors must keep pace with these changing conditions, as we participate in certain vital stages of them". The Ince Report (1945) proposes a compulsory assessment of all school leavers with regard to health, ability and aptitude, so that the child, in friendly discussion with his teacher and parent, can be advised on the type of job in which he will do best and be happiest. The Youth Employment Service will help the school leaver to find this job, and if it is not available in the neighbourhood it will supply money to enable the youth to begin his career away from home. No longer will the boy with artistic gifts, living in a colliery village in Wales, have of necessity to work down a pit, he will be encouraged to develop his aptitude perhaps as an architect in Lancashire, or as a designer of textiles in Yorkshire. Just as juveniles are prohibited from working with machines dangerous to their fingers and with chemicals dangerous to their eyes or skin, so the Ince Report seeks to prohibit their work in dead-end jobs dangerous to their developing skill and brain; the worst dead-end jobs should be filled by natural dead-enders of all ages.

NATIONAL SERVICE

This subject cannot be left without reference to a new and important factor in the life of our adolescents. After their eighteenth birthday boys have to register for eighteen months' National Service. Deferment is granted to apprentices and students to allow them first to complete their course of training. It is also granted to certain of those employed in the essential and undermanned industries of coal mining, cotton, agriculture and merchant service. Of those medically examined for the Services, 13 per cent. were found unfit.

We do not yet fully realize what may be the effects of peace-time conscription for the first time in British history. We do know that some employers are naturally loath to engage seventeen-year old boys when they know they may be called up within twelve months, and the boy leaving school at fifteen is apt to feel unsettled. He is unable to plan for five years ahead when he leaves the Service at the age of twenty. With only the present marginal difference between skilled and unskilled rates of pay, many boys are unwilling to embark on long apprenticeship schemes which may be interrupted by their call-up, whilst the higher piece work rates often tempt them into short-term unskilled work. On the other hand, the deferment scheme may encourage some boys to settle down to complete their apprenticeships, later to continue their craft in skilled Service jobs. Intending university students may sit for their Higher School Certificate under the threat that a few awkward questions may mean postponement of their entry into the university until they have spent two years in uniform. This

adults except by invitation, buy their own movie magazines and jazz records. They should elect representatives to the Works Committee *pro rata* to the proportion of juvenile labour employed. By this democratic training they will be helped to reach social maturity. Fleming (1948) shows that the demands of adolescence are for a chance to help in the welfare and running of some group, at home, at school, at games or at work. The juvenile desires to be accepted by society, to be included in the gang, and to feel that his job is worth while. He also expects to be treated for what he is—a budding adult.

Morris (1947) shows the difficulties for both foremen and juveniles to work together happily in the authoritarian structure of industry. The 1946 Report by H.M. Chief Inspector of Factories states that foremen attribute the high accident rate of juveniles to lack of discipline among modern adolescents, which is due to slackening in parental control. Surely the problem is not that of adolescence but of unenlightened adult supervisors, and this may cast some light on the 40 per cent. labour loss among our probationer nurses. When adolescents (or adults) feel that they are an essential unit in the team and can see that their job counts, working morale will improve. The mental health of any community is indivisible.

THE CHANGING BACKGROUND OF SCHOOL AND WORK

Today, labour is the most valuable raw material in industry. This fact forces more and more mechanization and further breakdown of jobs into simple, rapid repetition. One skilled fitter can set and maintain machines for ten unskilled workers to feed. With new machines, coal mining demands less skill from the collier. In a survey of 2,200 jobs in eighteen American industries, Bell (1948) found that under one week's training was required for 70 per cent. of the jobs, and over four weeks in only 20 per cent. Elton Mayo (1948) advocates fewer long apprenticeship schemes and suggests that trainees should be more adaptable to a wide variety of modern machinery so that they can switch with the changing needs of modern industry. The loss of the satisfaction derived from skilled work in a craft will be compensated partly by the satisfaction of the smooth running of an efficient plant, but chiefly by the deeper satisfaction from a fuller participation with responsibility in the society of the workshop, the whole factory and in the community.

Training for this fuller life will be the responsibility of County Colleges as well as of industry itself. Already in Britain the 1944 Education Act coming into force this year will screen all school children at the age of eleven, diverting the academic cream towards the grammar school *en route* for the university, and guiding the children with practical ability towards technical colleges, whilst leaving the main stream to pass to the modern school until the age of fifteen. The adolescent in his last term at school is now visiting factories to see the conditions of future jobs. Youth

THE ADOLESCENT DELINQUENT BOY

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INCLUDED here as "delinquent" are those boys of fourteen to seventeen who are deemed to be in need of care or protection, or who are proved to be beyond the control of their parents, as well as those who have been found guilty of committing an offence. Any kind of generalization is extremely dangerous. There does not exist a delinquent type, but the delinquent boy is just an ordinary boy, the product either of his environment, including his family relationship and training in his home, or of some peculiarity in himself, such as his poor intelligence or his own unhappiness, or of a combination of both his environment and of his personality.

ENVIRONMENT

It is not often that a delinquent boy of average mental ability comes from a really well-ordered home, with wise and united parents who live in a district which has open spaces for play and is devoid of slums. On the other hand, a large number come from homes which are overcrowded, inadequately furnished and neglected. They will have had little home life. From early childhood they have dragged themselves up in the street which became their nursery and remains their playground in adolescence. There they have been unsupervised and uncontrolled, and they have got into the habit of doing whatever they want to do just whenever they want to do it. There is no privacy in their home, no sense of ownership—beds are shared, clothes are shared, the chest of drawers is shared. It is difficult to take a pride in oneself or in one's belongings, and to have a sense of "mine" and "thine". This sense is also lacking in those boys who have been brought up in orphanages and institutions which make inadequate provision to give each boy a feeling of individuality and of ownership.

The extraordinary stupidity and poor intelligence of one or both of their parents are very marked. Many are quite incapable of rearing their children wisely, or of good housekeeping. They are slipshod and unreliable in everything—their spending and their earning, their meals, their cleanliness and their tempers. The father is often in casual labour, and the mother is too busy with household work to take proper care of the children. Very often she herself goes out to work during the hours that she is most needed by her children at home, sometimes in order to supplement her husband's earnings, although sometimes quite unnecessarily, as though she were seeking a means of escape from the drudgery of her home duties. Many have been brought up without themselves having attained the habit of self-control. An example of this unrestrained impulsiveness is to be found in

new transition in later adolescence may be as serious as the earlier change from school to work. It affects almost two-thirds of all boys from the age of eighteen to twenty. The lad leaves the 44-hour week of hard work in industry, exhorted and geared to the increasing tempo for rising exports, to find in his new life, time lying heavily on his hands. Recent correspondence in *The Times* from magistrates perturbed by the increase in juvenile crime in Hampshire, provoked the reply by the Director of Public Relations, that the War Office is "alive to its responsibility for protecting the morals and for employing to advantage the spare time of its young soldiers". National Service provides an opportunity to continue, rather than interrupt, the process of maturing by broad education on the vocational, cultural and physical sides.

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sometimes hatred for the other become more pronounced. It is no less painful for him to live in an atmosphere of parental discord, where continuous quarrelling takes place between his mother and father, whose own unhappiness is reflected in him, driving him to seek some form of escape.

Many are fatherless children whose mothers either over-indulge them with love or else are incapable of understanding or disciplining them, and the boy takes advantage of his mother's weaknesses and gets beyond her control. The over-possessiveness of some mothers who make excessive demands on him causes the boy to rebel against her as he grows older. In many instances the parent with whom he lives has re-married or is cohabiting. The boy, if he is old enough to remember his other parent, resents this. He is unhappy and seeks to escape from his unhappiness in adventurous misconduct. He feels that he is neither loved nor wanted. Some are illegitimate, or else the only reason for the parent's marriage was that the mother was pregnant at the time. In every marital dispute the boy is held to be the cause of the trouble and he is made to feel it and knows that he is unwanted.

Among the unhappy boys are those who returned after evacuation to discover that their parents had got used to living without them and that they were now in the way, or else that they themselves preferred living in the country with foster parents and were strangers in their own homes. This insecurity intensified their adolescent instability. Some, after being the only or youngest child for many years, become jealous of a later born child and feel that they have lost the attention which their mothers at one time devoted to them. This also makes the boy feel unwanted and unloved.

The worst disability a child can suffer is indifference in the home, whether it be imaginary or real. To feel starved of love and understanding creates in him an attitude of not minding what happens, for he thinks that no one really cares. Thus he becomes a liar or a thief. He will even behave badly simply to draw attention to himself in his loneliness. Delinquency in such cases of unhappiness is an escape from an emotionally intolerable situation. Antisocial behaviour in the adolescent is often a sign of distress, due to his failure to achieve certain fundamental needs in life, the principal ones of which are to be loved, to feel secure, to be recognized as an individual personality, to be accepted as a valuable member of the community, to be respected as an individual, and to gain success in at least some enterprise in life.

EDUCATION

A large number of delinquent boys are well below the average in intelligence; many are borderline "educationally subnormal" (E.S.N.). They are incapable of reasoning about the rightfulness of what they do and of looking ahead to see the consequences of their actions. They are easily led by others, and because of their stupidity are the more likely to be caught. Many still coming before the Courts left school when they were fourteen: that most unstable and changing period when they so much needed guidance and friendship to help them through the early years of puberty. Raising the

the way children urinate on the curb of the pavement whenever they have the inclination to do so. That so many adolescents are enuretic is partly due to bad domestic habits—in many slum dwellings the lavatory is in the yard, uninviting on a cold night—though nearly always there are also psychological or physical causes.

The discipline in such homes has been uneven. It has depended upon the temper and the health of the parents. Sometimes a boy will have been reprimanded or chastised for acts which on the next occasion are passed over, so that he grows up to have no fixed standard of what is right and what is wrong. One parent will permit what another forbids and he quickly learns to play one off against the other; one will over-indulge and the other will be too strict; the boy will be shielded, often with lies and deceit, from the ire of one parent by the other. He has never quite known what to expect. When he has been punished, the punishment has consisted of a "belting" or a smack on the face, given in anger and not as a deterrent training and, if he has been troublesome as a youngster, given so often as to have become quite ineffective. He will have been constantly threatened, but he never knew whether the threats would be carried out.

This same inconsistency in training is noticeable with regard to his pocket money, which has a strong bearing on delinquency. It will have been irregular, not because there was insufficient money to give to him but because the whole management of the household has been unordered and disorganized. The result is that he has never learnt how to save nor how to spend. The money has been given to him for a specific purpose—to buy sweets or to go to the movies—and he spent the whole of it on that purpose. If he wanted more, he asked and then whined for it, or else he got a tip for some errand done for a neighbour. As a working boy he is rarely given pocket money by his parents, but usually takes a liberal portion of his wages for "spending money". He has little idea of wise spending, and in satisfying his immediate whims and needs, it soon comes to an end—but not his needs! He is too old to whine for more and is not likely to be able or willing to supplement it by extra work. He therefore finds other ways of obtaining it, either by unlawfully taking things which he can exchange for money or by stealing the things he actually wants. Untrained in self-control, he does what he wants to do without reference to an ethical code of right and wrong and with no thought of the rights of others. He does not look or plan further than the satisfaction of his immediate desires. His excuse is that "it was a sudden temptation".

FAMILY RELATIONSHIP

Perhaps more important than the material conditions of his home is the broken family relationships which may exist among the rich or the poor. A high percentage come from broken homes or where there is some degree of marriage disharmony. The parents may be divorced or legally separated or merely living apart. The boy has divided loyalties so far as his parents are concerned, and as he passes through adolescence, his loyalty for one and

kept at home by their parents to run errands or to look after the children, or they have deliberately truanted as an escape from their own unhappiness. Unless these backward boys receive special tuition, they grow up with a deep sense of inferiority to the other boys in the class and with a desire to compensate for it. Some are even unable to read or write. There is inadequate provision made for those who have been ascertained as E.S.N., some of whom require boarding school education. Unhappiness at their failure to enjoy the work in school may be one of the reasons for truancy. There is a close relationship between truancy and delinquency. Unfortunately, many of the boys do not come before the Juvenile Court until playing truant has become a habit, as the procedure is that the parents are first summoned to the Petty Sessional Court, and it may be several months before the boys are referred to the Juvenile Court. They have got used to deceiving their parents about school and to wasting the day aimlessly wandering about the streets, where their unhappiness grows deeper, or where they pick up with undesirable companions or find excitement in illegal acts.

EMPLOYMENT

This attitude towards school, together with the lack of training in the home, is reflected in the employment record of many adolescent delinquents. Either because of their lack of foresight or because of the poverty of their homes, they tend to enter blind-alley jobs with high wages rather than to learn a trade which would give them prospects for the future but low wages at first. They are constantly changing their employment. A fair number lose their job through bad timekeeping, or else they stop away from it in the same way as they had truanted from school. Afraid to tell their parents, they deceive them by pretending to set out for work each day, taking their fare money and food with them. At the end of the week they steal in order to bring home their "wages". They rarely take an interest in their work and look upon it merely as a means for gaining a livelihood. The knowledge that they will be called up to the Forces at eighteen has an unsettling effect on many. It does not seem to them worthwhile to settle down and persevere in their work.

LEISURE

New experiences, adventure and competition are for most boys essential to happiness, and if they cannot be attained in desirable ways, the boy will seek to get them in antisocial ways. Boys' Clubs should be able to provide opportunities for healthy experiences of this kind, but it is generally extremely difficult for them to absorb a delinquent of this type, and very few boys who appear in the Court are active members of boys' organizations. Having been nurtured in the undisciplined atmosphere of the street, he finds irksome even the free discipline of the club. He does not understand, nor does he easily have loyalty to, the corporate group of the club. Never having acquired the habit of doing anything systematically and regularly, except to attend school by compulsion, he rebels against regular attendance

leaving age to fifteen should eventually assist in that respect. At present they are unused to the new Act and tend to revolt against remaining at school for another year.

One of the main features in training the characters of boys in the Public Schools has been that they have learnt that they have to do the things that they are required to do, even though it be at a time when they do not feel in the mood to do them. This sense of obligation has been instilled into them not only by their masters, but also by the other boys in the House or College. To adhere to the rules and traditions of the School has become a habit with them. This sense of obligation on the one hand, and of community loyalty on the other, are seldom learnt through continuous practice by the boys who leave the modern secondary schools, and if neither has been taught him in the home, they are never likely to become a habit in later life. Deprived of such habits, the undisciplined boy from a bad environment indulges himself as and when he likes. He does not fear the disapproval of his mates, who are more likely to praise him than to reprimand him for his exploits, nor does he feel a sense of loyalty to the community; he only fears being caught and punished.

His knowledge of religion is lamentably poor and what little he has is generally absurdly perverted: it is limited by what he has learnt in school, and it has little restraining influence on him, nor is it an inspiration to him for right doing. Like many others of the same age, he is seldom an active member of a Church and he does not realize that the great moral laws have a Divine sanction. The theory that the end justifies the means is one that he often hears and which indirectly influences his actions, and especially his truthfulness. The general deterioration in commercial morality since the war affects him. When there are so many regulations, he is continually hearing discussions as to how they can be evaded rather than as to how they can be kept. His father or older brothers will also have learnt in the Forces that it is praiseworthy to "make" things in war. As in the years after the 1914-18 war, another generation exists which is adept in scrounging. Those boys who saw wholesale destruction during the war do not consider it wrong to break or destroy.

All these tendencies are counteracted for the boy from a good home, where his moral standards have been taught him by example even more than by precept. Many delinquent boys will find no such example in their homes, where the standard of truthfulness and honesty, and of sex and ethical morality are often the exact opposite to what they should strive to follow. Some parents are convicted of receiving the goods which the boys have been found guilty of stealing. A great many boys come from homes where at least one other member of the family has been in trouble.

The training in school is therefore of paramount importance. Many with apparently poor intelligence are mentally retarded rather than educationally subnormal. Apart from the interrupted education during the war, a large number of such boys have attended school irregularly; they have either been

MENTAL DISORDERS IN ADOLESCENCE

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ALL discussions upon this subject are faced at the outset with the metaphor of the melting pot. It is true that many of our character traits have been formed by the time adolescence is reached. Yet it would be an arrogant physician who would claim that even when given all the detail of extensive personal and family history he could invariably forecast the outcome. Constable said no one could paint a landscape who was not reverent before Nature, and it is doubtful if any can help the young unless their dealings are at least tinged with awe.

THE PROBLEM

Throughout adolescence reactions to physical, intellectual, and emotional stresses are constant, and they weave and interweave in countless ways. When these stresses are most marked because of under- or over-development of the intelligence, or because of emotional overfeeding or starvation, there are three main results which may be observed:—

(1) The vast majority of potential psychiatric misfits in adolescence will continue to battle through, with or without obvious scars. But it is likely that this number may be reduced for three reasons: (a) Psychiatric or psychosomatic symptoms may arouse more attention. If the National Health Service is efficient, that alone should cause an increased awareness. (b) Enrolment for National Service, with its screening methods, has already hinted at the size of the problem, quite apart from regrettable Service experience. (c) New educational openings and family ambition are likely to impose stresses to which, formerly, less fully educated children were not prone. Wisdom must learn to steer her course between the danger of sniffing psychiatric trouble everywhere, and the equally distorted assertion that these dangers do not exist. The argument from "our grandfather's time" is inept: our grandfathers' problems were very different.

(2) The second reaction may be described as the "notoriety reactions", i.e., those in which the patient forces himself upon others' attention by striking symptoms which may be clearly neurotic or more subtle compromises, such as excessively bad work, untidiness, or irresponsibility. The same disorder may be seen in outspoken delinquency, stealing, truancy, frauds, fantastic tales and claims, and sexual precocity.

(3) The third reaction is the reverse: the withdrawal syndrome—apathy, dreaminess, stupor, fugues—before the responsibility and threats of manhood.

All these deviations expose defective adjustments to society. In minor mental disorder or in psychosis the individual fails socially. The mature

at a voluntary organization. He prefers to be unrestrained rather than to submit to the traditions of behaviour in the club. He will take part in various activities but will not stick to them. His instability and lack of concentration are more marked than in the other members. If he is below the average in intelligence, he feels a sense of inferiority, and either he leaves the club because he is unhappy in it and does not fit in, or else he compensates for his inferiority by making such a fearful nuisance of himself that he has to be turned out of the club.

Sheer boredom leads many into adventurous exploits. The normal club boy satisfies his competitive instincts in team games; the other satisfies it by competing against the police. The risk incurred by climbing dangerously up drain pipes and across the roofs provides him with a satisfying excitement, quite apart from the prize he expects to win from a successful break-in. He prefers to lead what he calls a "smashing life" with a constant round of the cinemas, dance halls, cafés and billiard saloons. When his cash is low, he stands with his mates in groups at the street corners, trying to look tough and indulging in a good deal of horse play, especially with girls. He has few friends but many acquaintances with whom he tries to ingratiate himself by generous treating to cigarettes, a meal or a cinema. A good deal of his spending money goes in this way and on clothes, usually a loud suit of the latest pattern and cut, with flashy tie and socks which demand attention from the passer-by and compensates for his feelings of inferiority and unwantedness. He mixes with a gang rather than with one particular pal. He prefers to be with boys and only goes with girls in the hope of getting some sex experiences. He has seldom had any instruction in sex and has no sense of chivalry or ideals of fatherhood and married life. His knowledge of sex has been picked up; he has probably never learnt the right attitude to girls, and the type of girl with whom he mixes has been brought up in the same ignorance.

SUMMARY

Except for those who are psychopathic personalities, or are ascertained as E.S.N. or certified as mentally deficient, the outlook for the adolescent delinquent is a good one. Some are willing to be guided by an understanding Probation Officer, whose friendship with the family as well as with the boy himself may result in a happy adjustment to the family relationship. When this is not possible, an ordered life in a hostel or an approved school can give him that sense of security which may have been lacking, and provide for him a standard of morals of which he was ignorant or which he had been too weak to try to achieve. In the community life of the school or hostel he learns unselfishness and loyalty and his obligations to others. Under constant supervision he can be helped to discipline himself. Unless the stupidity, ignorance and low moral standards of the boy or his parents are so deep-rooted as to make reformation almost impossible, there is an excellent chance of the adolescent delinquent boy making good and of his becoming the worthy citizen which the vast majority are capable of being.

with apparently normal histories may develop phobias or hysterical compromises. They require adequate psychotherapy. The psychopath presents the picture of endless changes at work or of mates, and deficient appreciation of the social implications of his conduct. The very permanence of the symptom, his inability to form warm attachments with appropriate give and take, make the psychiatric supervision of the psychopath more difficult than the active treatment of a cooperative neurotic.

It is in adolescence that the psychopath reveals himself first: wilful youth, or restless, possibly nymphomaniac, girl. He has hitherto been sheltered by parents or teachers. In adolescence he must face responsibility for his own acts, and he evades this. It is remarkable that he practically never becomes psychotic: this may be a matter of genetics; it may be that he cannot register the emotional conflict which is apparent as a precipitating cause in many breakdowns. Thus, in what follows, a psychopathic personality may also be mentally dull or backward, but he does not show fugues, depressions, excitements or clear-cut schizophrenia. He often makes suicidal threats; he shows psychosomatic disorders with an hysterical colouring. He rarely experiences the acuter anxieties and panics.

THE MENTALLY DULL AND DEFECTIVE

It is too little realized that mental dullness is a much more serious social and medical problem than actual defect. The defective is an individual whose mental capacity only reaches that of a nine-year-old normal child. No amount of training will make him more resilient. He can accept long periods of dull work, and in this way differs from the restless changeability of his younger normal brother. Such thinking as he does for himself will be slow, although his actions may be quick. He may be ready in following easily understood commands. His powers of criticism are poor: he may be stimulated by suggestion into stupid or even criminal actions. The defective by no means always looks dull. Some even scintillate in expression, but they produce few spontaneous ideas. They may have well-developed dog-like loyalty and hence be excellent workers at simple unskilled jobs. Temperamentally they may be placid or, like many whose defects are not mental but visual or aural, suspicious, irritable, jealous. What is true of the defective, who constitutes about one in every hundred of the population, is to a less extent true of the dull and backward, whose numbers are almost twenty times as great. When such persons live among others equally handicapped, any psychiatric problems which arise are no more common than in any other strata of intelligence. The matter is far otherwise when the sporadically occurring backward child is born to parents of high intelligence, or to those who, although of average intelligence, are ambitious, or have purposely limited their family for this one ewe lamb. The disappointments of school life may have been weathered but the idea that the youth only consorts with those of lower classes (though of intelligence only equal to his own), prefers the low-brow to the Third Programme, or shows no aptitude even at semi-skilled

adolescent has learnt that:

"The game is more than the player of the game,
And the ship is more than the crew".

Modern education as well as modern standards of discipline have tended to ensure that individual achievement in class or in factory should be aimed at. How often have ex-Servicemen claimed "we didn't accept the offer of a stripe because it would limit our freedom or impose responsibility".

I recently saw a fifteen-year-old girl whose reports over several years exuded "excellents" and "very good" and which never once hinted that the child was a lone soul without friend or foe, a cipher, a potential candidate for the most serious of disorders, schizophrenia.

Intellectual achievement is not to be equated more highly than social adaptability, and the demagogues will have failed us until they have striven for and ensured a proper set of values.

The mental disorders most often met with, exclusive of the psychoneuroses, i.e. psychosomatic disorders, anxiety and obsessional states pure and simple, are:—(1) The psychopathic personality; (2) the mentally dull and defective; (3) suicidal threats and suicidal attempts; (4) the fugues; (5) depressions; (6) excitements; (7) schizoid and schizophrenic states.

THE PSYCHOPATHIC PERSONALITY

This term, now so widely used, covers conditions which twenty years ago were described as "emotional mental defect". I do not wish to bemoan the loss of that difficult term. Nevertheless, correctly understood it was useful, for the psychopathic personality is defective in his emotional maturity. He has not learnt how to discipline the demands of his self to the needs of his family or of the wider society in which he lives. He wants the "here and now" which we realize is normal in a child of five, but abnormal in the youth of fifteen. Appeals to his altruism, and punishment, fail to check his courses.

The psychopathic personality may be a delinquent; he is more often just a chronic disturber of his family's peace—a spendthrift, a rolling stone, an alcoholic, abnormally boisterous and aggressive, sexually promiscuous, or a perversionist. He may occur in every walk in life; he may be a dullard, he may be an artist, he may be of high intelligence, or indeed a genius. The distinguishing marks are two: (1) his complete inability to care about the distress he gives himself or others, despite protestations to the contrary; (2) his inability to alter his conduct as the result of punishment.

The psychopath may present himself because of his disturbing behaviour; he may present himself because of neurotic symptoms, especially hysterical compromises when his demands are not granted, e.g. suicidal gestures or incapacitating psychosomatic disorders, such as vomiting attacks. More common are phobic manifestations, claustrophobic symptoms, seldom crippling but used by him to demand altered conditions at work or in the home.

It is, in my view, essential that the term psychopathic personality be restricted to such cases as have shown chronic social defectiveness. Persons

well be found to be ashamed, and in no likely condition to repeat the gesture.

Treatment.—How can the threat of the frustrated best be dealt with? In my view, there should be a period of sleep, deepened by a strong hypnotic (sodium amytal 6 grains [0.4 g.], or medinal 5 grains [0.32 g.], or alternatively, paraldehyde 120 minims [8 ml.]), immediately following a discussion of the deed. Once there has been a short but adequate rest, a quick return to school, office or factory should be the sequel. A wary, but not too conspicuous eye, should be kept upon developments. In the preliminary discussion it is best to side with the victim, emphasizing that action has resulted from false premises: things are probably less black than they are painted. Caveat the attitude of scorn, the attitude of moral indignation, or the appeal "Look how you have disturbed so and so". The most hysterical adolescent has a reason for the most stupid act. In a matter of real seriousness the reason must be honoured to begin with; it will not be altered by mirth or morality alone.

FUGUES

The decision as to whether a person has had a fugue, or has been a truant or a deserter is sometimes difficult to make. In the latter two cases a good deal of truculence and general stupidity under examination may be revealed. The true fugueur gives, when examined, a picture of confusion, or altered consciousness, or the first observer's story gives this clue.

Whereas a truancy merits the sort of treatment that was indicated for the suicidal gesture of the frustrated youngster, a fugue necessitates psychiatric attention. However purposeful its motive, a situation which allows the individual to act as a dual personality, with his normal "knowing" self in abeyance, arises from serious mental disturbance. The old idea that fugues were "hysterical" phenomena, although true in a psychopathological sense, is too facile in a clinical sense. Most fugueurs would have made a suicidal gesture had the fugue not prevented their "knowing" selves from carrying out their intent. Further, only the psychiatrist can judge how far the individual should be pressed to confide his secret, or made (after, say, an evipan analysis) to face his problem.

DEPRESSIONS

True endogenous depressions are seldom met with in mental hospitals before the age of twenty-one. I believe that they occur outside hospitals more frequently, but are usually short-lived, such is the resilience of youth. Conditions closely allied to endogenous depressions, such as states of depersonalization or reactive depressions are much more common.

EXCITEMENTS

Acute mania and katatonic excitements are far more frequent than endogenous depressions at this age. They may be exceedingly dramatic in onset with no prodromal symptoms. Restless activity and over-talkativeness pass

jobs, creates a vortex of family excitement in which parental disappointment, unrewarded patience, self-criticism and renewed criticism of the young are inextricably mixed with filial amazement, misunderstanding, frustration, and resentment. All such situations may be solved in any of the three general ways already indicated. Delinquency or withdrawal are not surprising.

It may be emphasized at once that the oft-repeated "He could do better if he tried", or parental discourses upon laziness, are as ineffective as they are unenlightened upon the true situation. How are such cases of dullness to be detected? They may be revealed by asking the youth to repeat seven digits, to subtract seven from 100, and seven from the remainder, and so on; to continue the series 1, 3, 5, 7, or 1, 4, 9, 16; to answer simple questions about current events or local geography; to see how readily he can tell in what way a book, a teacher and a newspaper, or a rose, a potato, and an elm tree are similar.

It is well to remember that since backwardness is so common, all doctors tend to forget that some medical instructions, for example, as regards infant feeding or nursing technique in the home, simple hygiene, or the application of liniments, to the mentally dull young mother are totally beyond her comprehension, and medical annoyance only makes confusion worse confounded. Similarly, whilst many backward patients respond warmly to their first days in hospital, others are over-anxious and may even present a transient psychotic confusion which usually subsides quickly.

Stable defectives in simple jobs—labouring, domestic, laundry, or routine factory employment—stay. The unstable tend to drift from one occupation to another. Or their security may be threatened when they are hounded by desires for higher contributions to the family welfare. They are a menace as cranesmen, lorry drivers, or in more skilled pursuits where reactions must be quick, or dangers to themselves or others result. Of such material are constituted many of the accident-prone.

SUICIDAL THREATS AND GESTURES

The majority of attempted suicides in the young are not instances of the true insanities. They are reactions to frustrations: an ill-developed scheme for the solution of the difficulties, tinged not seldom with the expectation that the gesture will win some point not otherwise to be gained. The seriousness of the threat can never be lightly dismissed. Is a psychiatric examination of all such persons called for? Ideally, perhaps yes. But since such an ideal may be impracticable, what indications are there that one case is grave, or that another can be lightly dismissed?

I would emphasize that any youngsters whose behaviour when the general practitioner sees them is bizarre, furtive, or who when approached seem detached, or complain spontaneously that they or their surroundings are unreal, had best be seen by the specialist. The youngster who is frustrated rather than guilty, who is vocal or tearful rather than mute or furious may

attended with much suspicion of the parents, these interests also form a stepping-stone between the dependence upon authority in the schoolboy, and the independence and idealism of the adult.

In no set of symptoms during adolescence is the kindly interest of the general practitioner more necessary. Ideally, he should make time for these aloof or suspicious youngsters to come to his surgery, to have a word of interest and of cheer and, if he is in any doubt, to ask for a wise psychiatrist to see patient and parents. It is the family doctor who can reassure the parents, who is more likely than anyone else to get them to alter their coldness, or their demands, and to help the youngster if the symptoms are indeed those of adolescent anxiety rather than the beginnings of schizophrenia. If the signs of the disease are clear, no amount of parental fear, indifference or gross amblyopia should stand in the way of the doctor's insistence upon adequate hospital treatment.

NEUROTIC AND PSYCHOSOMATIC DISORDERS

Those syndromes so far described deal in the main with various manifestations of the *major* psychoses. I have not specified anxiety neurosis, reactive depressions, obsessional symptoms, or those psychosomatic disorders by which symptoms formerly called hysterical are now described.

To enumerate all these manifestations would take too much space. To begin with, the term *anxiety neurosis* is being gradually superseded by "reactive depression" or "affective disorder". In simplest terms there is a change of mood, clearly related to some topical problem, and associated with tears, despair, irritability, loss of sleep (usually at the beginning of the night). This may be the sole complaint. Attempts to solve the current conflict should be made. Commonsense advice with a few sleeping draughts may be all that is required to clear the symptom.

When the problem is more severe, somatic disorders may accompany the disordered mood. Loss of weight is common. Anorexia, gastro-intestinal upset, inframammary sensations, aches and pains, especially head "discomforts" and "backache", may be complained of rather than the altered mood. In my view many gynaecological complaints are primarily of this type. All these symptoms are in the first place an awareness of body function of which we usually take no notice, but which represents overaction of the sympathetic nervous system caused by stress. To the lay mind a symptom means physical disease, and in many practitioners' minds the idea that symptoms may be the result of an overactive sympathetic nervous system rather than of disordered organs only comes slowly. No one wishes to "miss" organic disease, especially in adolescence. Neither should anyone wish to "miss" functional disorders, since if they are treated by operations, or excessive investigation, the symptom may become "fixed" either in an adolescent hypochondriasis, or as a sort of alibi, recurring as a reason why adult problems can be evaded, or decisions postponed. This "fixation" of the symptom is what has occurred when psychosomatic disorder is present.

rapidly into a state of exaggerated sensitivity to any external stimuli, and there may be, or appear to be, vivid hallucinations. Forceful restraint is necessary, and intramuscular paraldehyde (10 ml.) is preferable to omnopon $\frac{1}{8}$ to $\frac{1}{2}$ of a grain [10 to 20 mg.] and hyoscine $\frac{1}{100}$ to $\frac{1}{75}$ of a grain (0.65 to 0.78 mg.). Rapid removal to a psychiatric unit is essential.

Not only are such attacks often fulminating, they may be exceedingly brief. They may result from stress or physical exhaustion; more often no satisfactory precipitating cause can be found. Pleas from relatives that John or Jean is less excited, and that hospital treatment is not called for should be resisted. Even if the lay conclusion is correct, after-nursing must be skilled.

SCHIZOID AND SCHIZOPHRENIC STATES

The schizophrenic disorders cover such a large field—emotional flattening, excessive day-dreaming, unproductive mental and physical activity, religiosity, excitement and stupor, florid or quiescent delusional symptoms, and others—it is surprising that not all adolescents show very brief symptoms of a schizoid type. There are brief periods in the lives of many adolescents when a small nexus of schizoid-like symptoms show themselves. How many have periods when they are quite abnormally suspicious of parents or friends, when they hold transient beliefs that they are talked of disparagingly, or that matters are arranged so as to discomfort them. How often are they religious, or so overcome with the excessive pursuit of physical perfection as to raise more than a smile in their elders. Sometimes, if these pursuits are not checked, religiosity passes on to delusions of mystical power; compulsive athletics on to hypochondriacal and astrological ideas about the body, mind, and spirit; normal adolescent sensitivity on to firmly held beliefs that the youngster emits fluids or odours of soul-saving or -destroying potency.

Such a summary shows something of the difficulties in determining in the young whether a grave or benign symptom is presented. In general, it is the absence of emotional warmth, of friends, of reasonable (not excessive) activities and pursuits, which heralds the insidious schizophrenic process: such is more likely to be the outcome in families where reason more than emotion flourishes, or where one parent is already "odd". Yet even so, I have to confess that some "potential schizophrenics", e.g., in homes riddled with ambition or with restriction, have shown remarkable plasticity and adjustment when their environment has been changed.

Treatment.—Prophylactic insulin comas can only be given in mental hospitals, and much resistance is often placed in the way of any such step. Psychotherapy directed to the formation of an affective bond between patient and doctor, whereby the youth feels that the doctor's place is to receive confidences rather than to probe deeply, and to be patient with suggestions for more outgoing activities, are techniques which do not require specialized psychiatric training, but ability to afford the time. Whilst interest in religion, philosophy, or politics may be the precursor of schizophrenia, and is often

INTRACRANIAL ANEURYSMS

A GENERAL SURVEY

By WALLACE B. HAMBY, M.D., F.A.C.S.

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IN 1761, Morgagni first described an aneurysm of the cerebral arteries found at autopsy, and seventeen years later Biumi (1778) of Milan described a fatal case of subarachnoid hæmorrhage originating from a ruptured arterial aneurysm. During the next century, whilst the pertinent continental medical literature emphasized cerebral aneurysms, the English concentrated on subarachnoid hæmorrhage. In 1859, Gull, of Guy's Hospital, correlated the two topics to show that subarachnoid hæmorrhage usually results from rupture of intracranial aneurysms. Interest in the subject declined until 1924, when Symonds, also of Guy's Hospital, again vitalized the topic. Since by this time neurosurgery had developed to the point where surgical exploration of the brain was safe, the lesions began to be found in the living patient. In 1934, Moniz introduced cerebral angiography, which made possible preoperative localization of the lesions. At present they are being recognized so often that a prominent Chicago neurosurgeon recently stated that, among patients admitted to his large teaching clinic, aneurysms rival neoplasms in numbers.

NON-FISTULOUS ANEURYSMS

There are several excellent classifications of intracranial aneurysms but, for clinical purposes, Jefferson's (1938) elaboration of Edwin Bramwell's classification of non-fistulous lesions is helpful:—

(1) Apoplectic type (producing subarachnoid hæmorrhage without localizing signs).

(2) Paralytic type:—

(a) Those with paralysis of cranial nerves, usually the third.

(b) Saccular (non-fistulous) aneurysms of the internal carotid artery within the cavernous sinus.

(c) Basal aneurysms affecting the visual pathways.

(1) *Apoplectic type*

Spontaneous subarachnoid hæmorrhage having no other obvious cause, such as trauma, septicæmia, or blood dyscrasia, usually and perhaps almost always comes from a ruptured "berry" (Collier, 1931) aneurysm lying in a bifurcation of, or along a vessel of, the circle of Willis. These are considered to be congenital or developing in a congenital defect in the vessel wall. They may be found complicated by arteriosclerosis, especially in older patients. Fortunately, the majority of these aneurysms, 87 per cent. in our series (Hamby, 1948), develop on the anterior half of the circle of Willis,

Here the bodily feeling or abnormal response is in the middle of the picture, the mood change is less obvious. Anxiety is localized upon the asthma, the pruritus, the vomiting, the giddiness, the pains or headache. The general anxiety and depression of reactive depression have been lost. Here we have the old "hysterical anorexia", dysmenorrhœa, psychogenic rheumatism, under a new guise. Such bodily manifestations of emotional distress or recurrent alarm may take protean forms. The essential point is that functional disorders in adolescence are quite as common as tuberculosis, peptic ulceration, sinus disease, gynæcological misplacements, and so forth, at this age. Psychic disturbances are much more probable than the minor abnormalities for which some surgeons, and indeed physicians, search.

Two other mental disorders require mention. First come the *phobias*, most often phobias of moving vehicles, restaurants, canteens and cinemas. Many other varieties exist—streets, churches, and animals; the condition may be completely crippling, or the phobia may have been evaded, e.g., the "tube-phobic" who spends much longer in getting to and from business on a bus. The second is the *unreality syndrome* in which the individual feels that external events and persons, or he himself, have become altered or unreal. These two conditions have this in common: they may both precede or lead insidiously into psychosis; they may both recede spontaneously. Neither condition is likely to clear by reassurance alone. Psychiatric aid should be sought.

Obsessive compulsive conditions, tics, aphonia, hysterical disorders of sensation and movement may all arise for the first time at this period.

What should be the practitioner's rôle when faced with any of these "neurotic" disorders? It is of primary importance that he should recognize the likelihood that the symptoms are emotional in origin. Confronted with symptoms of acute anxiety his aim is clear. By encouragement he will help the youngster to weather many storms if he can give the patient the feeling that the symptom is natural in the circumstances and that no moral turpitude is implied, e.g., when consulted about masturbation.

When the condition has progressed to psychosomatic disorder more of his time will be required. He will need to gain some insight into his patient's worries. Of these, the most common in adolescence are the struggle between the youngster's aims and his (perhaps) limited potentialities: the struggle to fulfil his parents' hopes as compared with his own drives and inclinations; the difficulty in becoming a member of a group, in the school, in the suburb, in the factory, since for so many of us individual activities are so much easier than social responsibility and adaptability; difficulties in the sexual sphere, apprehension over menstruation and heterosexual friendships. If inquiries along these directions yield no light, or having been discussed produce no result, psychiatric help should be sought. It may well be that the doctor is doubtful of benefit—he might be equally dubious whether surgical interference for minor complaints will really cure, or whether bromides actually dissipate problems.

lesion may go unrecognized if a single cranial nerve is involved. Arteriography provides a convenient and trustworthy aid to diagnosis of these lesions. If the aneurysm is found in a position favourable for surgical attack, an attempt should be made to isolate it from the circulation, since otherwise it is a constant threat to the patient's life.

(b) *Saccular aneurysms of the internal carotid artery within the cavernous sinus.*—After it enters the skull, the internal carotid artery makes an "S"-shaped curve in the cavernous sinus. Here it is in intimate relation to the third, fourth and fifth cranial nerves and over the lateral surface of the sinus courses the fifth nerve. Within this small area an expanding lesion can produce a very complicated clinical picture. This was described first by Adams in 1869, then by Bartholow in 1872, and by Stopford in 1917, but has become known, especially by the continental writers, as the syndrome of Foix, who described it in 1922. The syndrome may be produced by neoplasms as well as by aneurysms. Aneurysms are more apt to expand rather abruptly, whereas the development of the syndrome is slower in the case of neoplasms. Jefferson (1937) further divided the syndrome into anterior, middle and posterior components by characteristic combinations of signs. From the therapeutic standpoint, such sharp subdivisions are hardly necessary, since the three areas lie within the same surgical field. Arteriography may be used to verify the lesion if it is suspected from its clinical manifestations. Otherwise, the surgeon, sharing the embarrassment of many of his illustrious forebears, may find himself in the unfortunate predicament of having opened an aneurysm in anticipation of removing a tumour.

(c) *Basal aneurysms with involvement of the visual apparatus.*—Jefferson (1937) has described these lesions in detail. Because of the relationships of the circle of Willis, aneurysms arising from that vascular circuit may compress the optic nerve, chiasma or tract. Clinically, the problem then becomes one of differentiating these lesions from tumours in the same area. The occurrence of subarachnoid hæmorrhage may provide the clue, otherwise arteriography will be needed for final confirmation.

PHYSICAL AIDS TO DIAGNOSIS

Roentgenography.—An aneurysm within the cranium, on the circle of Willis, will not impinge upon any portion of the skull; thus it will not disclose its presence by producing bony erosion. An aneurysm partly restrained against bone will erode it, so aneurysms of the carotid artery in the cavernous sinus may erode one side of the sella or the petrous tip. An aneurysm in the anterior portion of the sinus tends to erode and elevate the anterior clinoid process and to erode the superior orbital (sphenoidal) fissure and the optic foramen. Although sellar erosion may simulate that caused by pituitary tumours, it is usually sufficiently unilateral to put one on guard.

Rupture and stretching of the walls of a carotid aneurysm, with

where they are more accessible to surgical attack than are those on the posterior segment of the circle.

The clinical picture presented by this lesion is that of a sudden sub-arachnoid hæmorrhage occurring without obvious cause or pre-existing disease. The patient may be of any age, the peak or incidence in our series of 130 cases (Hamby, 1948) being at fifty years. If the hæmorrhage is of sufficient severity, death may be immediate. If it is of lesser intensity, the patient exhibits signs of meningeal irritation, severe headache, stiff neck, mild fever and variable neurological signs, depending upon the location of the lesion. The hæmorrhage may extend into the cerebral substance (52 per cent. of our autopsied cases) and produce evidence of cerebral damage. If the lesion bleeds no more, the spinal fluid becomes xanthochromic within seven to ten days and clear within three weeks. In our series, 52 per cent. of the patients had such a single hæmorrhage and 62 per cent. of these lived. The lesion may "leak" again or repeatedly while the patient is in the hospital, as in 48 per cent. of our patients; only 34.5 per cent. of these survived. The patient then makes a clinical recovery but may suffer a later attack. In our series, 75 per cent. of the patients were admitted in their initial attack and 55 per cent. of these survived. Of the 25 per cent. of our patients who were admitted in secondary (or further) attack, only 28 per cent. lived.

As emphasized by Richardson and Hyland (1941), a patient admitted in a primary attack of hæmorrhage should be kept in bed under basal living conditions, avoiding even the exertion of lifting his head, until his lesion has had a chance to heal solidly; a period estimated at from six to eight weeks. If any evidence of fresh hæmorrhage develops and fresh blood is found in the spinal fluid, the prognosis becomes decidedly worse. It is my impression at present that an arteriogram should be done at this time to see if the lesion is one that may be controlled surgically. Indeed, as Wechsler and Gross (1948) have shown, this procedure may be done safely at any stage in the attack; it may be advisable as soon as blood is found in the spinal fluid.

(2) *Paralytic type*

(a) *Aneurysms with paralysis of cranial nerves.*—The congenital saccular aneurysms that involve the intracranial carotid artery and its branches, or the fusiform, predominantly arteriosclerotic aneurysms of the vertebral-basilar segment of the circle of Willis, may compress cranial nerves and indicate their presence by the resulting paralysis of function. This may consist of mere dilatation of a pupil, or of paralysis of an extrinsic eye muscle producing diplopia, or of pain in the trigeminal distribution. The large fusiform lesions in the posterior fossa may even simulate neoplasms by their involvement of several adjacent nerves. If the aneurysm bleeds, the associated nerve paralysis will suggest not only the etiology, but also the location of the lesion. Unless this possibility is kept in mind, the unruptured

Dott (1933) has described a method of reinforcing the walls of these lesions by wrapping them with muscle strips, but the treatment is probably at least as hazardous as leaving the lesion alone.

If the aneurysm involves the anterior communicating artery, surgical intervention is again very hazardous. Aneurysms with well-developed necks may be clipped off. If they rupture while being handled, control of the ensuing hæmorrhage all too often requires closure of both anterior cerebral arteries on each side of the aneurysm. We have been forced to do this on three occasions, with two deaths, and the surviving patient paraplegic and practically amental.

Blood flow through the circle of Willis.—Under normal conditions the major portion of each cerebral hemisphere is supplied by the ipsilateral internal carotid artery, whilst the brain stem, cerebellum and occipital lobes are supplied by the vertebral-basilar complex. The circle of Willis is a potential collateral channel by which ideally the entire brain might be supplied in the event that one major afferent artery was occluded. Circles of Willis are variable anatomically and in their efficiency of distribution of blood flow to the two sides of the brain. In the so-called "normal", but rather "ideal", circle the two sides receive equal volumes of blood from the two carotids and the communicating vessels are competent to supply both sides if either of the carotids should be occluded. Unfortunately, in an appreciable number of people, one or more of the communicating vessels are lacking or are incompetent for their tasks, or one carotid is inadequate to supply the required blood flow to both cerebral hemispheres. In these cases occlusion of a carotid artery would result in a cerebral catastrophe.

It is important then, to test the efficiency of the circle of Willis before closing any of its afferent vessels. Clinically, the Matas test is used for this purpose.

The common carotid artery is compressed with the thumb against the vertebral column and occlusion is tested by cessation of pulsation of the superficial temporal artery. Occlusion is maintained for ten minutes. If no symptoms develop that are referable to the ipsilateral cerebral hemisphere, it may be assumed that ligation of this vessel would not be attended by any ischæmia of the brain.

Perhaps a more certain test for competence of the circle of Willis may be made by arteriography.

If one carotid is injected while the other is occluded manually, both anterior cerebral and perhaps both middle cerebral arteries also are filled and are visualized on the films. This would indicate that this artery is competent to irrigate both sides of the brain. If such filling cannot be obtained, ligation of the vessel is hazardous. In some cases a collateral circulation found inadequate by the Matas test may be improved by gradually increasing periods of compression of the artery until its occlusion no longer produces symptoms.

All non-fistulous types.—After dealing with the acute subarachnoid hæmorrhage and locating the lesion, the apoplectic and non-apoplectic types of non-fistulous aneurysms are treated alike: they must be excluded from the cerebral circulation.

subsequent connective tissue repair, is often associated with deposition of calcium salts. These may be deposited in small flakes or in broad sheets that curve round the parasellar area in somewhat characteristic fashion. Jefferson (1938) has estimated from his cases that about five years is required for sufficient calcium to be deposited to permit visualization of the plaques.

Cerebral angiography.—If a radio-opaque solution is injected rapidly into an internal carotid artery and a series of skiagrams is made before it leaves the vessels, an excellent view can be obtained of the major and minor arteries of that side of the brain. The method was developed by Egas Moniz (1934) and has become widely employed in the diagnosis of all types of intracranial lesion. Obviously its greatest usefulness is in the field of intracranial vascular lesions. Dandy (1935) of Baltimore, a pioneer in intracranial vascular surgery, was not impressed by the procedure. He believed that too often thrombosis within an aneurysm would prevent visualization of the lesion, thus producing false negative evidence. His chief interest, however, was in the lesions near the base of the skull, where they are likely to produce rather characteristic clinical signs. Many of the small "berry" aneurysms, especially those associated with hæmorrhage, have been disclosed in this manner when no clinical clue to their position could be found.

Angiography can be done in most cases by puncturing the carotid artery with a needle introduced through the skin, or the vessel can be exposed surgically. One of the chief advantages of the closed, or "percutaneous" method is that the test is likely to be employed more often than when the neck must be opened, thus leading to the disclosure of more lesions. Moreover, bilateral injections are more likely to be done with this than with the "open" technique. At the present stage of development of knowledge of the subject, it is my impression that in almost all cases, it is advisable to obtain anteroposterior and lateral views of the vessels of each side of the brain. This is true particularly of cases of subarachnoid hæmorrhage; in an appreciable number of these cases, bilateral aneurysms are present and preoperative knowledge of this fact may alter surgical judgment.

TREATMENT

The apoplectic type.—As suggested earlier, the patient with a single, primary hæmorrhage may be allowed an opportunity to heal under a regimen of simple bed rest for eight weeks. If he already has had a previous hæmorrhage or if the lesion bleeds more than once while under observation, his prognosis becomes so poor that an attempt should be made to localize the lesion and to isolate it from the circulation. Arteriographic visualization of the lesion is of great value in planning the surgical attack. If the aneurysm is on the carotid artery or in such a place on the circle of Willis that the involved artery can be occluded without endangering blood flow to the ipsilateral hemisphere, the lesion can be cured by placing hæmostatic metallic clips on each side of the aneurysm; or if the lesion has a neck that can be clipped off, circulation through the parent vessel may be preserved. If the lesion lies on the middle cerebral artery, however, the parent vessel cannot be clipped off without disaster to the major portion of that cerebral hemisphere.

Treatment.—In the earlier and more benign states of development of these lesions treatment may be entirely symptomatic, directed especially to the control of convulsive seizures. In the past, surgeons have been reluctant to attack these lesions because of the danger of uncontrollable hæmorrhage, but recent reports (Pilcher, 1946; Trupp and Sachs, 1948) suggest that many of them may benefit from coagulation of the vessels or from complete excision of the mass.

(2) *Carotid-cavernous fistula*

Before the carotid artery enters the cranial cavity it traverses the cavernous sinus. If an aneurysm ruptures here or if the artery is ruptured by trauma (most of these lesions follow a head injury), arterial blood flows directly into the sinus. The ipsilateral eye protrudes and pulsates because of arterial blood flow into the ophthalmic veins. The eye is usually fixed in its orbit and the patient suffers pain over the first and second trigeminal divisions. The eye may be rendered blind at the moment of rupture, but vision may be preserved. Chemosis of the conjunctiva may lead to orbital infection. The patient is at first annoyed and finally made frantic by the never ceasing machine-like bruit caused by the pulsing blood flow. This can be stopped temporarily by manual occlusion of the carotid artery in the neck.

Treatment.—A few of these lesions will heal spontaneously and a few have healed after the application of mechanical compressors over the carotid artery in the neck. In the majority of cases, however, the fistula must be isolated from the blood stream surgically. In 1809, Benjamin Travers first successfully ligated the common carotid artery for the relief of pulsating exophthalmos. Most of these lesions can be cured by ligation of the internal carotid artery in the neck, after the Matas test has indicated the safety of the occlusion.

In some cases such ligation will stop the symptoms only for a few days, after which they recur and progress. This is because the lesion is still being supplied with arterial blood from above *via* the circle of Willis; as collateral circulation improves, blood loss through the fistula increases. In this event, the carotid must be occluded above the sinus to prevent the fistula from taking from the circle of Willis blood that is needed to supply the brain.

In 1911, Zeller tied the carotid intracranially above the cavernous sinus for the first time, but the ligature was accidentally torn through the artery and the patient bled to death on the operating table. While I was assisting him, Gardner first successfully ligated the intracranial carotid with silk (Hamby and Gardner, 1933). In 1935, Dandy reported closing the artery with a silver clip above the sinus and this has become the standard procedure.

Since the cavernous sinus pressure is lower than diastolic blood pressure, the fistula encourages progressive development of collaterals to feed it. Thus even ligation above and below the sinus may not suffice; the ligation of the external and internal carotids of both sides has been necessary to effect a cure in some cases.

Aneurysms of the internal carotid artery below the bifurcation into anterior and middle cerebral may be treated by occlusion of the ipsilateral internal carotid artery in the neck. Occlusion of this vessel may be followed by late (six to twenty-four hours) cerebral complications, believed by many to be caused by thrombosis ascending from the site of ligation. This has led Dandy (1944) to advocate occluding the vessel intracranially above the lesion before tying it in the neck. Recent work by Sweet and Bennett (1948) on direct pressure readings in the internal carotid after occlusion below that level suggests that occlusion of the vessel in the neck ensures reduction of pressure and pulsation to a safe level in the distal portion of the artery. From the review of large series of cases and on speculative grounds an idea has developed that occlusion of the common carotid artery is safer than of the internal, assuming that a reflux of blood flow from the external into the internal carotid may provide a greater factor of safety. Sweet's studies seem to disprove the idea entirely and to indicate that internal carotid ligation is the procedure of choice. A factor of great importance is the method of ligation. Abrupt ligature ligation so injures the intima that thrombosis is the rule. Ligation by fascia, as advocated by Dandy (1935), by plication as practiced by Poppen (1949), or by tantalum clips as by Sweet (1948) and others, is less likely to be complicated by thrombosis. Preliminary partial occlusion followed in seven to ten days by complete occlusion may prove to be the safest method of all. If the aneurysm is on the circle of Willis in such a position that it can be excluded from the circulation without impairing blood flow into either middle cerebral artery, it should be so attacked by craniotomy.

INTRACRANIAL ARTERIOVENOUS FISTULÆ

Direct blood flow from an artery into a vein in the cranium may occur in (1) cortical arteriovenous anomalies, and (2) in carotid-cavernous fistulæ (pulsating exophthalmos).

(1) *Cortical arteriovenous anomalies*

These lesions are caused by an arrest in development at the embryonic level of direct connexion of arterial and venous vessels without intervening capillaries. The communications gradually widen until the surge of arterial blood into the veins mechanically irritates the cerebral cortex or progressively interferes with its circulation. The patient then begins to have focal or Jacksonian convulsive seizures and later may develop other neurological signs. By arteriography, Wechsler and Gross (1948) have found a number of cases of subarachnoid hæmorrhage caused by bleeding of such lesions. The patient may hear a bruit in his head and this may be heard with a stethoscope. Calcium may be deposited around the vessels so that the lesion becomes demonstrable on skiagrams. Finally, the diagnosis may be verified by arteriography.

Treatment.—In the earlier and more benign states of development of these lesions treatment may be entirely symptomatic, directed especially to the control of convulsive seizures. In the past, surgeons have been reluctant to attack these lesions because of the danger of uncontrollable hæmorrhage, but recent reports (Pilcher, 1946; Trupp and Sachs, 1948) suggest that many of them may benefit from coagulation of the vessels or from complete excision of the mass.

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CONCLUSION

Although aneurysms of the brain are, and will continue to be, lesions attended with danger to the patient's life and cerebral function, encouragement can be gained from widening clinical appreciation and recognition of the entity. With better methods for precise diagnosis and localization, it is reasonable to anticipate progressively improving therapy. The fact must, however, be recognized, that in some instances peoples' brains, as well as their residences, are endowed with such faulty plumbing systems that only replacement will give satisfactory results. At present, no such replacement being available for the cerebrum, much care must be exercised to use the material at hand as wisely as possible.

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THE NATIONAL FORMULARY, 1949

By WILLIAM A. R. THOMSON, M.D.

THIS Formulary has been prepared by a Joint Formulary Committee consisting of representatives of the Royal College of Physicians, the British Medical Association, the Ministry of Health, the Admiralty, the War Office, and the Pharmaceutical Society. According to a communication from the Ministry of Health, "the Minister has decided to accept this for use in the National Health Service" in England and Wales, but in the preface it is stated that "the prescriber is in no way limited to the preparations in the Formulary [and] it is not suggested that hospitals should restrict the range of preparations in use". The Formulary, which will replace the National War Formulary, will come into operation on May 1, 1949. It is intended that "every doctor, chemist (including suppliers of surgical appliances) and dentist participating in the National Health Service shall have a copy".*

THE CONTENTS

The aim of the Joint Formulary Committee has been to produce "a volume of convenient size which may be carried in the pocket or kept ready at hand by the practitioner and pharmacist". In addition to the detailed formulæ, there is a host of notes which will prove of value. These include notes on the barbiturates, enemas, hormones, liver therapy, and sulphonamides, but not penicillin or its preparations. The section on liver therapy includes references to folic acid, but not to the use of hog stomach extracts. Other useful notes deal with prescriptions for dangerous drugs and for schedule poisons, a partial list of proprietary preparations, and metric and imperial equivalents. There will be many who will regret that the imperial system only is used in the formulæ. It does seem a pity that the example of the *British Pharmacopœia* has not been followed, and that all formulæ are not given in both the imperial and the metric systems. Practitioners can scarcely be expected to take seriously the plea for the general and gradual adoption of the metric system when an official publication such as this adheres to the old imperial system.

SOME INNOVATIONS AND OMISSIONS

The two most interesting innovations are the introduction of two new titles. In order to distinguish them from powders (*Pulveres*) intended for

* Additional copies may be obtained direct from the publishers: The British Medical Association, Tavistock Square, London, W.C.1, and the Pharmaceutical Press, 17 Bloomsbury Square, London, W.C.1, price 2s. 6d. post free. Interleaved copies are 4s. post free.

internal use, dusting-powders have been given the latin title of "Conspersi". Incidentally, it is interesting to note that, although in the general notices it is recommended that solids should be prescribed in grains (gr.) and ounces (oz.), the amount of dusting-powder (and powder) to be dispensed, unless otherwise directed, is given as "960 gr.". It would be interesting to know why this is not stated in the much simpler form of "2 oz." or "60 g.". The formulæ of six dusting-powders are given, including *Conspersus dicophani*, the synonym for which is "DDT dusting-powder":—

Dicophane	96 grains (6.2 g.)
Calcium carbonate	96 grains (6.2 g.)
Light kaolin	to 960 grains (62 g.)

Compound zinc powder, or zinc, starch and boric powder, are now replaced by *Conspersus zinci oxidi et amyli compositus*:—

Zinc oxide	240 grains (15.5 g.)
Starch, in powder	240 grains (15.5 g.)
Purified talc	240 grains (15.5 g.)
Boric acid, in powder	to 960 grains (62 g.)

It is also stated that when dusting-powder is prescribed, *Conspersus talci borici* shall be dispensed:—

Boric acid, in powder	96 grains (6.2 g.)
Starch, in powder	96 grains (6.2 g.)
Purified talc	to 960 grains (62 g.)

The other innovation is the use of the term "vitrellæ" to describe small crushable glass capsules containing drugs such as amyl nitrite. In this way it is hoped to differentiate clearly from soluble gelatin capsules (Capsulæ) and the inhalations (Vapores). Three vitrellæ are included in the Formulary: amyl nitrite (containing 3 or 5 minims [0.2 or 0.3 ml.]); octyl nitrite (containing 3 minims [0.2 ml.]); and trichloroethylene (containing 1 ml.).

The two striking omissions from the Formulary are heroin and bismuth carbonate, a curious pair of bedfellows to receive such simultaneous dismissal. The former, with its preparations, has been excluded as part of the united international attack on this drug because of its dangerous habit-forming potentialities. Although many experienced practitioners will still continue to use heroin, including the linctus, in suitable cases, the Committee has undoubtedly been right in its decision to emphasize the caution necessary in using it by insisting that practitioners be required to prescribe it on an individual basis. Bismuth carbonate, as a constituent of mixtures and powders for gastro-intestinal disorders, has been under a cloud for some time, and most practitioners have become so used to prescribing its equivalents that there will be few who will shed many tears over its omission.

APPLICATIONS

By an interesting coincidence, the first item in the general section of the

Formulary—that devoted to “Applications”—is the most up-to-date of the whole Formulary. It contains only four preparations, but all are of recent innovation:—

Benzyl benzoate application:

Benzyl benzoate	1 oz. (28.4 g.)
Emulsifying wax	35 grains (2.3 g.)
Water	to 4 fl. oz. (114 ml.)

Detergent application:

Methyl hydroxybenzoate	2 grains (0.12 g.)
Emulsifying wax	52 grains (3.4 g.)
Yellow soft paraffin	35 grains (2.3 g.)
Arachis oil	80 minims (4.7 ml.)
Water	to 8 fl. oz. (227 ml.)

This is intended for removing fatty ointments from the skin.

DDT application:

Dicophane	17½ grains (1.1 g.)
Emulsifying wax	35 grains (2.3 g.)
Xylene	145 minims (8.5 ml.)
Oil of citronella	5 minims (0.3 ml.)
Water	to 2 fl. oz. (57 ml.)

Lethane application:

Lethane 384 special	1 fl. oz. (28.5 ml.)
White mineral oil	1 fl. oz. (28.5 ml.)

(Boiling-point not below 325°)

CAPSULES

Of the six capsules, four contain vitamins. Of these the most interesting is the Vitamin Capsule:—

Vitamin A	2,500 units
Aneurine hydrochloride	0.5 mg.
Riboflavine	0.5 mg.
Nicotinamide	7.5 mg.
Ascorbic acid	15 mg.
Vitamin D	300 units

The recommended dose is 2 or 3 capsules daily.

CREAMS

These include aminacrine cream (obstetric cream) and proflavine cream. The formula of the former is:—

Aminacrine hydrochloride	2 grains (0.12 g.)
Glycerin	24 minims (1.6 ml.)
Sterculia gum	30 grains (2 g.)
Chlorocresol	1 grain (60 mg.)
Industrial methylated spirit	48 minims (3.2 ml.)
Distilled water	to 2 fl. oz. (57 ml.)

It is stated that, although this cream is not a general bactericide, it may be effective against hæmolytic streptococci and *Ps. pyocyanea*.

internal use, dusting-powders have been given the latin title of "Conspersi". Incidentally, it is interesting to note that, although in the general notices it is recommended that solids should be prescribed in grains (gr.) and ounces (oz.), the amount of dusting-powder (and powder) to be dispensed, unless otherwise directed, is given as "960 gr.". It would be interesting to know why this is not stated in the much simpler form of "2 oz." or "60 g.". The formulæ of six dusting-powders are given, including *Conspersus dicophani*, the synonym for which is "DDT dusting-powder":—

Dicophane	96 grains (6.2 g.)
Calcium carbonate	96 grains (6.2 g.)
Light kaolin	to 960 grains (62 g.)

Compound zinc powder, or zinc, starch and boric powder, are now replaced by *Conspersus zinci oxidi et amyli compositus*:—

Zinc oxide	240 grains (15.5 g.)
Starch, in powder	240 grains (15.5 g.)
Purified talc	240 grains (15.5 g.)
Boric acid, in powder	to 960 grains (62 g.)

It is also stated that when dusting-powder is prescribed, *Conspersus talci boricus* shall be dispensed:—

Boric acid, in powder	96 grains (6.2 g.)
Starch, in powder	96 grains (6.2 g.)
Purified talc	to 960 grains (62 g.)

The other innovation is the use of the term "vitrellæ" to describe small crushable glass capsules containing drugs such as amyl nitrite. In this way it is hoped to differentiate clearly from soluble gelatin capsules (Capsulæ) and the inhalations (Vapores). Three vitrellæ are included in the Formulary: amyl nitrite (containing 3 or 5 minims [0.2 or 0.3 ml.]); octyl nitrite (containing 3 minims [0.2 ml.]); and trichloroethylene (containing 1 ml.).

The two striking omissions from the Formulary are heroin and bismuth carbonate, a curious pair of bedfellows to receive such simultaneous dismissal. The former, with its preparations, has been excluded as part of the united international attack on this drug because of its dangerous habit-forming potentialities. Although many experienced practitioners will still continue to use heroin, including the linctus, in suitable cases, the Committee has undoubtedly been right in its decision to emphasize the caution necessary in using it by insisting that practitioners be required to prescribe it on an individual basis. Bismuth carbonate, as a constituent of mixtures and powders for gastro-intestinal disorders, has been under a cloud for some time, and most practitioners have become so used to prescribing its equivalents that there will be few who will shed many tears over its omission.

APPLICATIONS

By an interesting coincidence, the first item in the general section of the

and glycerin lotion, and evaporating lead lotion. Dalibour water, i.e. copper-zinc lotion, is also mentioned, as well as calamine lotion and oily calamine lotion.

MIXTURES

These call for little comment. In future, when "mistura expectorans" is prescribed, the following compound ammonium and ipecacuanha mixture is to be prescribed:—

Ammonium carbonate, B.P. 1932	3 grains (0.2 g.)
Tincture of ipecacuanha	10 minims (0.6 ml.)
Liquid extract of liquorice	10 minims (0.6 ml.)
Anise water	60 minims (4 ml.)
Camphor water	120 minims (8 ml.)
Water	to ½ fl. oz. (14 ml.)

There are five mixtures containing potassium bromide, including a compound gelsemium and hyoscine mixture. In spite of recent work suggesting that potassium salts have toxic potentialities, both a potassium citrate mixture and a potassium and hyoscyamine mixture are included, each containing 30 grains (2 g.) of potassium citrate and 15 grains (1 g.) of potassium bicarbonate.

NASAL DROPS

This section is introduced by a warning that "caution should be used in prescribing oily nasal drops, since the oil is said to retard the ciliary action of the mucosa of the respiratory tract and the drops of oil may enter the trachea; prolonged and continued use may cause lipoidal pneumonia. Accordingly only four formulæ for nasal drops are presented and ephedrine nasal drops have been replaced by an ephedrine spray".

PAINTS

These include the popular Mandl's paint, phenol with camphor paint, and Whitehead's varnish. In addition, formulæ are given for Castellani's paint (also known as magenta paint), solution of brilliant green and crystal violet (now referred to as *Pigmentum tinctorium*) and triple dye (or compound crystal violet paint). The formula for the magenta paint is:—

Magenta	1½ grains (0.11 g.)
Phenol	17½ grains (1.1 g.)
Boric acid	3½ grains (0.22 g.)
Resorcinol	35 grains (2.3 g.)
Acetone	20 minims (1.3 ml.)
Industrial methylated spirit	40 minims (2.6 ml.)
Water	to 480 minims (28.4 ml.)

It is pointed out that this paint should be protected from the light.

The formula for proflavine cream is:—

Proflavine hemisulphate	1 grain (60 mg.)
Chlorocresol	1 grain (60 mg.)
White beeswax	22 grains (1.4 g.)
Wool fat	44 grains (2.8 g.)
Distilled water	230 minims (13.6 ml.)
Liquid paraffin	to 2 fl. oz. (57 ml.)

In future this cream is to be dispensed when acriflavine cream or emulsion of acriflavine is prescribed.

EYE-DROPS

The twenty-three eye-drops, for which formulæ are given, provide a comprehensive list, of which the following may be given as examples:—

Lachesine eye-drops

Lachesine chloride	1 grain (60 mg.)
Solution for eye-drops	to 120 minims (8 ml.)

Proflavine eye-drops

Proflavine hemisulphate	3/100 grain (1.8 mg.)
Distilled water	to 120 minims (8 ml.)

There is both a strong and a weak sulphacetamide eye-drop, the former containing 30 per cent., and the latter 10 per cent. of sulphacetamide sodium. The formula for the solution for eye-drops which is used to make up many of the drops is:—

Methyl hydroxybenzoate	2 grains (0.12 g.)
Propyl hydroxybenzoate	1 grain (60 mg.)
Distilled water, freshly boiled and cooled	to 20 fl. oz. (570 ml.)

INJECTIONS

It is a sign of the times that the injections outweigh the mixtures by almost 3:2, there being sixty-two injections as compared with only forty-four mixtures. Respiratory stimulants are well represented by lobeline, nikethamide, and picrotoxin. Insulin and protamine zinc insulin are both included, but not globin insulin. There will be many, especially pædiatricians, who will regret that no injection of a water-soluble vitamin K is included. Only the official injection of menaphthone, containing 5 mg. of menaphthone per ml. in ethyl oleate or "a soluble oil", is included.

LINIMENTS AND LOTIONS

Tradition predominates in these two sections. All seven liniments are well-tried preparations, such as A.B.C. liniment (equal volumes of liniment of aconite, liniment of belladonna and liniment of chloroform), camphorated oil (20 per cent. w/w of camphor in arachis oil) and "Lin. meth. salicyl" (25 per cent. v/v of methyl salicylate in arachis oil, cottonseed oil or rape oil). Lead still holds pride of place among the lotions, with lead lotion, lead

CURRENT THERAPEUTICS

XVI.—ANTIMALARIAL DRUGS

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UNTIL the discovery of pamaquine in 1926, quinine was practically the only specific antimalarial drug known. Since then, however, large numbers of synthetic substances have been examined for antimalarial properties, and many compounds have been shown to have activity, either in bird, monkey or human malaria, or in all of them. The volume of work on this subject may be estimated from the American research done during the recent world war, in the course of which something like 14,000 different substances were synthesized and tested in one way or another for antimalarial activity. Similar work on a much smaller scale was carried on in Germany and England during the war. It would be out of place here to attempt a summary of such work. From the practical point of view it is necessary to consider only the six most active compounds which are in common use.

There is in existence no single antimalarial drug which is perfect in human malaria. That is to say, there is no drug which can always be relied upon in all circumstances to act as a true preventive against infection, to cure the clinical attack, and to prevent subsequent relapses. Nevertheless, there are at least three modern synthetic drugs which in some respects are superior to quinine in the treatment of human malaria. In certain circumstances these compounds approximate to the ideal antimalarial but, taken by and large, they all fail at some major point; for instance, none can deal unaided with the important problem of relapsing vivax malaria.

This article is written with a view to assisting the practitioner in dealing with a case of malaria as he is likely to see it. Each drug is discussed separately, and a final summary is given which is meant as a practical illustration of modern usage of antimalarial drugs. Only vivax (benign tertian) and falciparum (malignant tertian) malaria are discussed; in general it may be said that the two other forms behave in a manner similar to vivax malaria.

QUININE

Quinine is a bitter, colourless, crystalline alkaloid usually prepared as the bihydrochloride, the hydrochloride or the bisulphate. Of these salts the first is the most soluble. Quinine is prepared in the form of (a) tablets, each containing an amount of the salt equivalent to 4 or 5 grains (0.25 or 0.32 g.) of the alkaloid; (b) as powder in ampoules, prepared for solution in water: doses of 7.5, 9, 10 and 15 grains (0.5, 0.6, 0.65 and 1 g.) of the alkaloid are provided in this form; (c) solutions in ampoules: doses similar to (b).

PILLS AND TABLETS

Changing fashions in prescribing are well typified in the increasing use of tablets as exemplified in the Formulary. Whilst there are formulæ for eighty-eight tablets, there are only nine pills, and the once popular powder can only claim five formulæ (and two of these are for seidlitz powders!). Among the hoary Guy's pills, Bland's pills, and blue pills, the recently introduced pills of medicinal gentian violet look almost out of place. The tablets have a much more modern flavour, including as they do the three synthetic œstrogens—dienœstrol, hexœstrol and stilbœstrol; cyclobarbitone; mepacrine; methyltestosterone; methyl thiouracil, and the sulphonamides. It is also of interest to note that the hyoscine hydrobromide tablets are recommended for travel sickness: 2 tablets, each containing $1/200$ of a grain (0.3 mg.) to be taken one hour before travelling, followed by one tablet at intervals of six hours for a maximum of forty-eight hours, if necessary.

INFANTS' SECTION

This calls for little comment. It contains one dusting-powder ("Cord Powder"), one cream (the good old-fashioned zinc and castor oil cream), one emulsion (cod-liver oil), one enema (quassia), three linctuses, twenty-three mixtures, one pill (gentian violet), three syrups, and seven tablets. Many pædiatricians will question the need for including grey powder in the list, and the recommended prophylactic dose of ascorbic acid (5 mg. daily) scarcely seems in keeping with modern teaching. The most interesting mixture is the succinylsulphathiazole mixture:—

Succinylsulphathiazole, in fine powder	5 grains (0.3 g.)
Light kaolin	5 grains (0.3 g.)
Compound powder of tragacanth	$\frac{1}{2}$ grain (30 mg.)
Syrup of ginger	10 minims (0.6 ml.)
Emulsion of anise	1 minim (0.06 ml.)
Chloroform water	to 60 minims (4 ml.)

The recommended dosage is 120 minims (8 ml.) four times daily for children aged one to two years, and $\frac{1}{2}$ fluid ounce (14 ml.) four times daily for children aged three to five years.

ordinary therapeutic regimes. Very large doses may cause permanent blindness.

Dosage in children.—A child should be given quinine in doses roughly proportional to the body weight. As a simple working rule for children over five, the dosage may be calculated as one-twentieth of the adult dose multiplied by the age of the child in years. For instance, a child of five, supposing the adult dose was 20 grains (1.3 g.), would receive $20 \times \frac{5}{20}$, in other words 5 grains (0.32 g.).

MEPACRINE

(Atebrin, atabrine, quinacrine)

Mepacrine is a bitter, yellow, acridine dye prepared as the hydrochloride or methane sulphonate. It is prepared as (a) tablets, all of which contain 100 mg. of the base, usually made up as the hydrochloride, and (b) as a powder for solution, in the form of the soluble salt, methane sulphonate or "musionate"; each dose of this powder contains 300 mg. of the free base. Mepacrine is useful alone or in combination with quinine or paludrine. It is not customary to use it with pamaquine because it seems to heighten the toxic effect of the latter.

Oral administration.—Tablets break up easily in the gut. There is no need to crush them. They should be given with or immediately after food since, when given between meals, they occasionally cause some nausea and abdominal discomfort. Water should be taken freely with the tablets.

For treatment of an uncomplicated case of either vivax or falciparum malaria the following dose regime is usually satisfactory:—

300 mg. t.d.s., for the first, or first and second days;

200 mg. t.d.s., for the second or third days; and

100 mg. t.d.s., for the subsequent five days.

The high dosage in the first days of treatment is necessary in order to obtain the concentration in the tissues and plasma necessary for effective therapeutic activity.

For suppressive therapy 100 mg. daily should be taken. Both vivax and falciparum malaria are normally suppressed by this dosage. Radical cure is obtained in large numbers of falciparum cases, but not in vivax malaria.

Parenteral administration.—The indications for parenteral administration are the same as those for quinine. As a general rule, mepacrine should not be given intravenously. It is, however, a safe and successful drug to give intramuscularly. Given in this way it is less painful and less likely to cause abscesses than is the dihydrochloride of quinine.

The parenteral dosage is a single injection of 300 mg. of the base, given in the form of a solution of the methane sulphonate. The injection may be repeated in six hours but, as in the case of quinine, parenteral therapy should give way to oral as soon as possible.

Quinine is effective alone or in combination with mepacrine or pamaquine.

Oral administration.—Tablets of hydrochloride and bihydrochloride break up easily in the gut, and are given without crushing. The less soluble bisulphate is usually given in solution. Water should always be taken freely with the tablets. The dosage recommended for an uncomplicated case of vivax or falciparum malaria varies widely. A regime similar to the following is successful in most cases:—

Quinine, 10 grains (0.65 g.) t.d.s. for two days.

Quinine, 10 grains (0.65 g.) b.i.d. for five days.

For the suppression of malaria the dosage recommended is usually 4 to 10 grains (0.25 to 0.65 g.) daily, given usually as the easily soluble dihydrochloride. Both falciparum and vivax malaria are commonly but not invariably suppressed by daily quinine.

Parenteral administration.—The indications for parenteral administration are the same for quinine, mepacrine and paludrine, i.e., intractable vomiting, vascular collapse, coma, hyperpyrexia and hyperparasitæmia. Parenteral administration of quinine may be repeated once or twice at six- to twelve-hour intervals. Oral therapy should be substituted as early as possible.

Quinine may be given either intramuscularly or intravenously. Intramuscular injection is not popular in the British Empire because it is painful and muscle necrosis and abscesses may result in certain cases. Muscle necrosis is said to be more common when the dihydrochloride is used, since its solution is very acid. The Dutch recommend the use of the less acid solutions of the hydrochloride combined with urethane. The dosage given intramuscularly is the same as that given intravenously.

Intravenous quinine is widely used in serious cases. When the solution is administered slowly and well diluted, with reasonable aseptic precautions, there are no special risks. The dosage given intravenously varies from 7½ to 15 grains (0.5 to 1 g.) at a single injection, the dose depending upon the weight and clinical condition of the patient.

Effect on the parasite and clinical signs and symptoms.—Quinine is effective in curing the clinical attack in both falciparum and vivax malaria. Asexual parasites disappear within thirty-six to seventy-two hours. Sexual forms of vivax malaria take some days longer, and those of falciparum malaria are not affected. In both vivax and falciparum malaria the pyrexia is abolished within thirty-six to seventy-two hours from the beginning of treatment in the uncomplicated case. The patient feels better by the second or third day, and complicating factors, such as *herpes labialis*, usually clear rapidly. Quinine alone has no appreciable effect on the relapse rate of either vivax or falciparum malaria.

Toxicity.—There is some tinnitus, dizziness, and sometimes nausea with therapeutic dosages. These effects are not often severe but they may be present even with suppressive dosage. Skin sensitivity reactions sometimes appear. In large doses, quinine may cause abortion, but this is not likely on

grains (0.65 g.) of quinine or 100 mg. of paludrine, three times a day for ten days. It is not used for the suppression of malaria.

Effect on parasites and clinical signs and symptoms.—Pamaquine has a specific effect on sexual forms of vivax parasites. It has no effect on the sexual forms of falciparum malaria. The chief reason for its use, however, is its effect in reducing the relapse rate of vivax malaria. This effect was first shown by Sinton in India, and has been amply confirmed by experience in the recent war. Used with quinine or with paludrine it reduces the relapse rate of vivax malaria to less than 10 per cent.

Toxicity.—There is little margin of safety between therapeutic and toxic dosages. Pamaquine may give rise to cyanosis, and in therapeutic dosages may cause acute colicky abdominal pain. It is excreted in the urine and may give rise to renal obstruction from crystallization. Acute hæmolytic followed by hæmoglobinuria may occur, producing a clinical picture indistinguishable from that of blackwater fever. Patients receiving pamaquine should be treated in bed. They should be given plenty of fluid and the drug should be stopped at the first signs of toxicity.

Dosages in children.—Pamaquine should not be given to children.

PALUDRINE

Paludrine is a biguanide derivative synthesized in England in 1945. It is a colourless, bitter, crystalline substance and is usually administered as the hydrochloride. The more soluble acetate has been used for parenteral administration. It is prepared as tablets of the hydrochloride containing the equivalent of 100 mg. of the base.

Paludrine is a highly effective antimalarial drug and is successful when administered alone in the treatment of both vivax and falciparum malaria. It is an active suppressive in both vivax and falciparum malaria. In the latter it usually brings about radical cure and may act as a true causal prophylactic.

Oral administration.—The uncomplicated primary or the relapsing case of vivax malaria responds to a single dose of 300 mg. Subsequent treatment depends upon whether or not radical cure is aimed at, and is discussed on page 334.

Most uncomplicated cases of falciparum malaria will respond readily to 300 mg. twice a day for ten days. It has recently been found that some African strains do not react well to this treatment, but respond if the paludrine therapy is preceded by one single day's dosage with 900 mg. of mepacrine, administered as 300 mg. three times a day (see p. 334).

Suppressive dosage.—The standard suppressive dosage for both falciparum and vivax malaria for non-immunes is 100 mg. taken daily. For special purposes, for example, in a native labour unit, a single weekly dose of 300 mg. will provide a high degree of protection against both falciparum and vivax malaria.

Effect on parasites and clinical signs and symptoms.—When given in sufficient dosage, mepacrine will cure the clinical attack of vivax or falciparum malaria about as rapidly as quinine. The asexual parasites disappear in thirty-six to seventy-two hours. The sexual forms of vivax take some days longer to disappear and the drug has no effect on the sexual forms of falciparum. The temperature falls to within normal limits by the third day. Subjective improvement starts by the second or third day. Mepacrine produces radical cure in most cases of falciparum malaria but by itself has no apparent effect on the relapse rate of vivax malaria.

Toxicity.—A suppressive dosage of 100 mg. mepacrine daily has practically no side-effects. In a few individuals, after the first few doses, there may be slight abdominal discomfort and diarrhoea. During the war it was discovered that certain techniques of administration at intervals during the week could cause profound prostration accompanied by severe vomiting and abdominal distress. These regimes are no longer used.

In therapeutic dosages mepacrine is not toxic in the vast majority of cases. In some, however, towards the end of treatment severe temporary psychotic disturbances may occur, which disappear rapidly after the cessation of the drug. Mepacrine psychoses have not been reported on suppressive dosages. In high dosage, for instance, 1.5 g. or more at a single dose, mepacrine causes gastro-intestinal discomfort, vomiting and sometimes diarrhoea. Skin lesions closely resembling *lichen planus* have been observed in a few individuals who have taken suppressive mepacrine for some time. It has not yet been determined whether or not these can be related to mepacrine administration. Mepacrine can be taken continuously in doses of 100 mg. daily for many years without any noticeable effect other than yellow staining of the skin. Liver function is unaffected.

Dosage in children.—Up to the age of two years a child should not be given more than 150 mg. in twenty-four hours, but after this age the dose can be steadily increased to 300 mg. in twenty-four hours at the age of ten. A child of fifteen can be given the adult dose.

PAMAQUINE (Plasmoquin, plasmochine)

Pamaquine is a bitter, colourless, crystalline synthetic substance. It is an 8-amino-quinoline, and is thus derived from a portion of the quinine molecule. It is prepared as tablets of the hydrochloride or naphthoate. Each tablet contains 10 mg. of the base. Pamaquine is only administered orally; it is not given parenterally. It is now used only in combination with either quinine or paludrine, never alone.

Oral administration.—Pamaquine is used with quinine or paludrine with the object of reducing the relapse rate of vivax malaria. The usual dosage is 10 mg. of the base three times a day, given concurrently with either 10

malaria. Subjective improvement is rapid. On the whole it appears to be rather quicker than mepacrine, fever disappearing within forty-eight hours and asexual parasites within seventy-two hours. It has no effect on falciparum gametocytes.

Toxicity.—With therapeutic doses there may be slight toxic effects, chiefly dizziness, and occasionally erythema and mild cutaneous eruptions. The drug is tolerated well by pregnant women.

Dosage in children.—Children between the ages of five and fourteen respond to half the adult dosage without toxic effect. Information regarding younger age-groups is at present lacking.

PENTAQUINE (SN 13 276) AND ISOPENTAQUINE

These are 8-amino-quinolines and thus similar in chemical composition to pamaquine. Pentaquine is very active in avian malaria. In high dosages in man it acts as a causal prophylactic against the Chesson strain of vivax malaria. The prophylactic dose is, however, too toxic for ordinary use.

Like pamaquine, pentaquine is not used by itself, but is given in combination with quinine, in order to obtain both the rapid cure of the clinical attack and the reduction of relapse rate. Recent American work has indicated that isopentaquine is a safer drug than pentaquine because there is a greater range between the therapeutic and maximum tolerated dosages.

Concurrent administration of 10 mg. of pentaquine base and 330 mg. of quinine sulphate, four-hourly for fourteen days, has been shown to have a considerable effect in reducing the relapse rate of the Chesson vivax strain. (In vivax cases which relapsed after one course of treatment, a second course was found by Coggeshall to reduce the relapse rate to under 2 per cent.)

The dosage of 60 mg. of base daily produced toxic effects which were roughly equivalent to those experienced after 45 mg. of pamaquine base. Amongst the toxic effects noted were acute hæmolytic crises such as occur with pamaquine. In partially immune white subjects the daily dose of pentaquine could be halved and the toxicity was then practically *nil*.

This drug is still under trial.

THE CHOICE OF DRUGS

A glance at the foregoing brief summary of the properties of the available antimalarial drugs will show that although most are successful in certain respects, there are advantages and disadvantages in the use of each of them. It is now necessary to suggest lines of treatment in the more common malarial problems which are likely to arise.

The treatment of uncomplicated vivax malaria.—Irrespective of whether the case is a primary one or a relapse, clinical recovery from the acute attack can be almost certainly achieved, either by the administration of a full therapeutic course of mepacrine or by a single dose of 300 mg. of paludrine.

Effect on parasites and clinical signs and symptoms.—Some observers have reported that the cure of the clinical attack, especially in falciparum malaria, is somewhat slower with paludrine than it is with either quinine or mepacrine. In most cases, however, the asexual parasites disappear and the temperature falls by the third day. Most cases of falciparum malaria which respond to paludrine undergo radical cure. Paludrine does not radically cure vivax infections and when used alone does not affect the vivax relapse rate except in special circumstances.

Toxicity.—For all practical purposes paludrine can be considered a non-toxic drug. In some patients, however, on therapeutic dosage, there is some slight gastro-intestinal disturbance. This is never severe enough to require the cessation of treatment. Very large doses in adults and children have been followed by hæmaturia.

Dosage in children.—From birth to six years of age, 25 mg. per day may be given with safety. Between six to twelve years of age the dose can be raised to 50 mg. daily, and above the age of twelve the full adult suppressive dose may be given. Therapeutic dosage should be given to children in proportion to their body weight.

CHLOROQUINE (Resorchin, SN 7618)

Chloroquine is a 4-amino-quinoline compound first synthesized by German workers in 1937 and studied in America during the late war. It is usually prepared as tablets containing 250 mg. of the diphosphate, the equivalent of 150 mg. of the base. It is more active than mepacrine in avian malaria. When used alone it is successful in the treatment of acute attacks of vivax and falciparum malaria and as a suppressive in both forms.

Oral administration.—The use of chloroquine is still in an experimental stage but the following regime has been shown to be successful in both vivax and falciparum malaria:—On admission, 500 mg. of the diphosphate is administered, and this dose is repeated after four hours. A further 500 mg. is given on each of the following three days. A total of 2500 mg. of the diphosphate, the equivalent of 1500 mg. of the base, is thus administered in four days.

Chloroquine is used as a suppressive in both falciparum and vivax malaria. Radical cure is often obtained in falciparum malaria, but the drug has apparently no effect on vivax relapses. Dosage for suppression has not yet been fully worked out, but it has been shown that a single dose of 500 mg. of the diphosphate, given once a week, is effective in both falciparum and vivax malaria. No firm information is available concerning the use of chloroquine parenterally.

Effect on parasites and clinical signs and symptoms.—Chloroquine has an action very similar to that of mepacrine on both vivax and falciparum

slower acting than intravenous administration. Cases already complicated by blackwater fever should not be given quinine.

Treatment of vivax and falciparum malaria in indigenous populations in endemic areas.—In semi-immunes and immunes the signs and symptoms of malaria are usually mild and respond readily to a single oral dose of 300 mg. of paludrine. More severe cases have to be treated as for non-immunes.

Drug suppression of malaria.—For general purposes probably the best drug is paludrine taken in doses of 100 mg. daily. This is effective and non-toxic. It suppresses vivax malaria and produces radical cure, or acts as a prophylactic in most cases of falciparum malaria. Daily doses of 100 mg. of mepacrine have about the same effect. Paludrine, however, is superior to mepacrine in that it does not require a build-up dosage before exposure in an endemic area; dosage with paludrine may be begun on the day of arrival in the endemic area. Paludrine does not stain the skin and in this respect has a cosmetic advantage over mepacrine, so far as women are concerned. In labour groups, where daily dosage is often administratively difficult, a single weekly dose of 300 mg. of paludrine will produce a high degree of protection. A single weekly dose of 500 mg. of mepacrine has a similar effect. In some cases daily dosage with either paludrine or mepacrine fails to suppress falciparum malaria. This occurs particularly in subjects who have already been heavily infected before the suppressive regime is begun. It is therefore essential in dealing with those who have been exposed in endemic and hyperendemic areas to attempt to eradicate the falciparum infection before beginning suppressive therapy. A full course of either paludrine, paludrine plus mepacrine, or mepacrine, is therefore indicated before institution of suppressive therapy.

Chloroquine has been used with considerable success for the suppression of both falciparum and vivax malaria. It may prove better than the other drugs mentioned in that it need be given only once a week to obtain the highest degree of suppression. It has not yet been proved that the effect of this single weekly dose is much superior to that of paludrine.

In either case relapses will occur. The chances of relapse can be minimized by the administration of combined courses of either quinine and pamaquine or paludrine and pamaquine, as described on page 330. A good deal more information regarding pentaquine and isopentaquine is needed before these drugs can be recommended for general use.

At first sight it might be considered that an attempt should always be made to eradicate the infection and reduce the relapse rate in all cases of vivax malaria. It is certainly true that in a non-endemic area every endeavour should be made to get rid of the infection, but in an endemic area, and particularly in a hyperendemic area, this may not be good policy. The treatment of each attack with a combined course containing pamaquine might be both uneconomical and inadvisable because of the toxicity of the drug. In endemic areas, particularly when dealing with partial immunes, both among Europeans and indigenous populations, it is therefore probably wiser to rely on the effect of the single dose treatment with paludrine, followed by suppressive therapy.

Treatment of uncomplicated falciparum malaria.—There is considerable controversy on this point. On the one hand, some observers have found the administration of adequate doses of paludrine over a long enough period most successful in many strains of falciparum malaria. On the other hand, there have been failures with this dosage which has recently been found unsuccessful under experimental conditions in a West African strain investigated in England. It is also sometimes possible to increase artificially the insusceptibility to paludrine of a given strain of both vivax and falciparum parasites. It has therefore been suggested that in view of the possibility of the existence of non-reacting or resistant strains of falciparum, particularly in Africa, it might be wiser to reinforce paludrine therapy by the administration of 900 mg. of mepacrine on the first day of treatment. The non-reacting West African strain mentioned on page 331 was found to be susceptible to such combined treatment. Nevertheless, paludrine unaided brings about both clinical and radical cure in a wide range of strains of falciparum malaria. I use it as a routine in cases of falciparum malaria in seamen in this country, many of whom are suffering from their first attack. We have successfully treated in this way many patients who have acquired their infections in West and Central Africa, from the Belgian Congo to French Guinea.

Treatment of complicated falciparum malaria.—Severe cases of falciparum malaria, for example, those with high fever or in coma, or in which there is a high degree of parasitaemia, require urgent and immediate treatment. The choice lies between intravenous quinine and intramuscular mepacrine. The former is safe and rapid, except that there is a chance that blackwater fever may be precipitated in an irregular quinine taker. For this reason some workers prefer intramuscular mepacrine. Mepacrine acts at about the same point in the asexual life cycle as quinine but intramuscular injection may be

the value of the diaphoretic effect of a dose of antimony wine is forgotten. Many diaphoretics in larger doses increase bronchial secretion and may act as emetics. Some have an action on the heat-regulating centre; such are the coal tar derivatives which were introduced about 1890 and have enjoyed a wide popularity as analgesics. Their main action may be upon the heat centre, where they are supposed to lower the setting of the regulating mechanism, but they also produce a peripheral vasodilatation and an increased heat loss. Phenacetin, 5 to 10 grains (0.3 to 0.6 g.), is an effectual antipyretic, sedative and anodyne, but it can cause cyanosis by the formation of para-aminophenol, and susceptible persons develop erythematous rashes. Phenazone in similar doses has the same sort of actions, and amidopyrine, being less soluble, acts more slowly and for longer; but these drugs are dangerous in that they cause blood changes with a lowering of the leucocyte count.

It was in the year 1708 that Dr. Thomas Dover set sail from Bristol "for lawful trade and against the Queen's enemies in the South Seas". On this voyage he learned about the treatment of fever with ipecacuanha. He powdered the ipecacuanha root in a red-hot mortar with an equal quantity of opium and eight times as much saltpetre. Fever and dysentery were the common diseases on this voyage and Dr. Dover was very successful. He even rescued Robinson Crusoe from his lonely island. Since that time it has been recognized that ipecacuanha, or its active principle emetine, acts as a diaphoretic and makes a sick man much more comfortable. The dose of Dover's powder should be small, 5 grains (0.3 g.) is enough as a rule, and in any fever, or even the common cold, is most comforting, but the use of more efficient modern machinery has obviated the necessity of using saltpetre to produce a fine powder, so that now a mixture of 10 per cent. powdered opium, 10 per cent. powdered ipecacuanha and eighty parts of lactose is employed.

Alcohol is another well-tried diaphoretic. It is certainly useful in fevers and improves appetite when the acute illness has passed. Sweet spirit of nitre, which is an alcoholic solution of ethyl nitrate and other allied substances, is diaphoretic and diuretic and has a slight antipyretic action. Particularly useful for feverish children, it enjoyed a great reputation in the past, and it might with advantage be prescribed to-day.

Acetosalicilic acid and salicylates are especially interesting as antagonists of rheumatic fever; whether or not they are really specifics or mainly act by making the patient less reactive to the noxious causative agent, they are certainly the most effectual remedies in acute rheumatism. Fever is reduced, pain is relieved, joint swelling and redness disappear rapidly and the excessive perspiration is checked. Salicylates are absorbed rapidly, are excreted unchanged or conjugated with sulphuric or glycuronic acids in the urine and the sweat. It is not difficult to obtain a blood level of 15 mg. per cent., and by careful dosage more than twice this concentration can be maintained for some time. Occasionally one may see evidence of myocardial improvement by the disappearance of heart block in rheumatic carditis.

The hot sponge is the most simple and most efficient diaphoretic.

The skin may be reflexly stimulated and bronchial secretion increased by doses of antimonial wine, sweet spirits of nitre or tincture of ipecacuanha, which are especially useful in fevers in children. In all cases the cause of the fever should be attacked as vigorously as possible, but the personal comfort of the patient may be increased by diaphoretics:—

Powder of ipecacuanha and opium	5 to 10 grains (0.3 to 0.6 g.)
Tincture of ipecacuanha	10 to 30 minims (0.6 to 2.0 ml.)
Antimonial wine	10 to 30 minims (0.6 to 2.0 ml.)
Sweet spirit of nitre	15 to 60 minims (1.0 to 4.0 ml.)
Sodium salicylate	10 to 40 grains (0.6 to 2.5 g.)
"Disprin" (acetosalicylic acid)	5 to 15 grains (0.3 to 1 g.)

PROFESSOR K. DOUGLAS WILKINSON, O.B.E., M.D., F.R.C.P.

REVISION CORNER

DIAPHORETICS

THE constant and rapid changes of fashion in medicine may readily be observed in the variations in the popularity of the remedial preparations employed. To-day the word diaphoretic has almost completely disappeared, so that in the therapeutic index there is a jump from diamorphine to diarrhoea. In itself the omission may seem a small thing, but it reveals a curious lack of appreciation of therapeutic measures which may lead to a very real personal comfort in the feverish patient, and it savours of those laboratory pharmacologists who decry all therapeutic measures which cannot be estimated quantitatively.

"When any sick to me apply
I purges, bleeds or sweats 'em;
If after that they wish to die,
Well, verily! I. Lettsom."

Until the nineteenth century fever itself was a disease, the result of some sort of poisoning often, but not invariably, from the digestive tract. It was obvious that unsuitable food might prove so irritating as to cause vomiting or diarrhoea, and when less poisonous might lead to digestive upsets and fever. Reasoning from such premises doctors starved a fever and fed a cold until Robert Graves threw doubt upon the reasoning and stated that he would be satisfied with a simple epitaph "He fed fevers". Whatever their causation it was obvious that fevers differed in type: there were dry fevers in which the hot dry skin was characteristic, such was typhoid fever and "the pneumonia"; other fevers were accompanied by more or less perspiration, such were rheumatic fever, malaria, Malta fever and influenza. Among the many methods of treating a fever the chief were those mentioned by Lettsom, for the specific remedies were few; the red bark for the malaria and Dover's powder for the bloody flux; and although the more drastic or dramatic forms of treatment, purging and bleeding, were often used, no good physician was unaware of the value of diaphoresis.

THE THERAPEUTIC VALUE OF DIAPHORESIS

By increasing the action of the skin a large quantity of fluid may be eliminated, and not only fluid, but salt, urea, uric acid and other substances. Firemen working in a hot furnace room may become severely ill from dehydration or loss of salt, or both. The stoker who works in hot climates drinks salt water. Evaporation from the skin is the most effectual way of reducing temperature. Not only does it lessen the work of the kidney but it makes the patient more comfortable. In hot countries jugs are unglazed so that fluid percolates through the substance and evaporates on the surface of the container, thus keeping the contents cool. In India the patient with typhoid fever is sponged with iced water to reduce his fever. The greater the evaporation rate the greater the temperature reduction, so that even better results can be achieved by sponging with hot water. Cold sponging tends to reduce the blood supply to the surface of the body. Hot sponging, on the other hand, will dilate surface vessels and may induce natural perspiration even in the hot dry skin of the fevered patient.

THE ACTIONS OF DIAPHORETIC DRUGS

There are many drugs which produce a peripheral vasodilatation and so tend to reduce fever, the most famous historically being tartar emetic. Antimony salts are gastric irritants which reflexly cause an increase in the excretion of saliva, the bronchial glands and the skin, but most unfortunately these are poisonous and so difficult to detect that many notorious crimes have been carried out with this drug. Nowadays the antimony tartrate is used in the treatment of protozoal infections, and

TREATMENT OF INFECTED CORNS AND BURSAE

When the patient's symptoms are those of an infected corn or bursa, it is, of course, essential to clean up the infection before contemplating operation on the interphalangeal joint. If the infection is seen before suppuration has occurred, it will often clear up rapidly with rest, hot saline foot baths, antiphlogistine or kaolin poultices, and penicillin. It is often difficult to persuade a patient with a minor condition of this sort to rest properly, but unless he or she is prepared to give up walking about for a few days, cure may be very prolonged. Once suppuration has begun the pus-filled bursa beneath the corn should be drained by lateral incisions. It is wise to wait for at least two months after all infection has cleared up before contemplating an arthrodesis.

W. D. COLTART, M.B., F.R.C.S.

ASPHYXIA NEONATORUM

ASPHYXIA neonatorum may be defined as failure to establish normal respiration after birth, and includes foetal anoxia, primary respiratory failure, persistent atelectasis and respiratory obstruction in the newborn. Its exact incidence can be estimated only approximately, but it is a major cause of foetal and neonatal mortality, especially in premature infants, accounting for some 30 per cent. of stillbirths and early neonatal deaths. Even if the infant survives, permanent brain damage may result from severe and prolonged anoxia.

For normal extra-uterine respiration to occur, it is necessary that the respiratory centre of the foetus shall be capable of reacting to the physiological stimuli arising when the placental circulation is interrupted, that there shall be no obstruction to the entry of air into the lungs, and that the respiratory muscles shall be capable of effective movement.

CAUSAL FACTORS

The respiratory centre may be depressed by general maternal diseases, such as anaemia, which reduce the amount of oxygen reaching the placenta; by toxæmia of pregnancy causing inefficiency of the placenta itself; or by foetal disease, such as hæmolytic disease, reducing the transport of oxygen in the foetal blood. Analgesics and anæsthetics crossing the placenta and entering the foetal circulation may also depress the centre; in general, however, the effect of such drugs depends more upon the skill with which they are administered than upon the actual drug used, with the general proviso that morphine derivatives are especially dangerous to the foetus, particularly when given within a few hours of delivery. In prolonged labour, especially with early rupture of the membranes, uterine contractions may reduce the placental blood flow, either depressing the centre or stimulating it to premature activity according to the degree of anoxia produced. In the latter case there may be aspiration of sufficient liquor amnii to produce respiratory obstruction after birth. Cerebral hæmorrhage, or more commonly cerebral œdema, has a direct action on the cardiac and respiratory centres, and may result from difficult or prolonged labour.

Obstruction of the air passages is almost always due to excessive liquor amnii, vernix, mucus or blood. If this material penetrates to the finer bronchioles or alveoli, the resulting vernix membrane may give rise to asphyxial symptoms some days after birth. Infection is particularly liable to occur in these cases, with the production of broncho-pneumonia. A major factor in premature infants is weakness of the muscles of respiration, and this, with the immaturity of the respiratory centre, accounts for the greatly increased risk of asphyxia in these infants.

PREVENTION AND TREATMENT

It is obvious that the main preventive measures are obstetric. A reduction in the

HAMMER-TOE

THIS deformity most often affects the second toe. The toe is flexed at the proximal interphalangeal joint and the tip is usually extended, but may be flexed so that the nail comes to lie against the ground. Hammer-toe is often a bilateral condition and may affect the third toe as well as the second. There may be moderate hyperextension at the metatarso-phalangeal joint, but the condition of "hammer-toe" should be distinguished from that of "claw toes" in which there is gross hyperextension of all the toes at the metatarsal joints. "Claw toe" is part of a deformity of the whole foot known as pes cavus.

ETIOLOGY

The cause of the deformity is often obscure. Sometimes it is congenital and then the tip of the toe is flexed. In acquired deformities, tight socks and short shoes have been blamed. There is often a hammer deformity of the second toe in cases of hallux valgus.

SYMPTOMS

The patients are often children and in many the toe is causing no trouble. Symptoms arise from pressure on the dorsal surface of the proximal interphalangeal joint, where a bursa, or callus, or both, may form. When the tip of the toe is flexed a corn may form or the nail become thickened and painful. Often the corn and bursa, which lie under the proximal interphalangeal joint, become infected, and the patient will complain of pain from them. The infection may be of an acute or chronic nature, and in the acute cases suppuration will often occur and an abscess form in the bursa.

In hallux valgus the second toe may be pushed backwards to such an extent that the proximal phalanx is dislocated on to the upper surface of the metatarsal head. The patient will then complain of metatarsalgia.

TREATMENT

Attempts to correct the deformity in children by stretching, strapping, and splinting invariably fail, although it may be that the parents will insist that "something must be done". Chiropody is useful for the patient who cannot or will not submit to operation.

Operations described consist essentially in arthrodesis of the proximal interphalangeal joint, with excision of enough skin, capsule and bone to allow the toe to become straight. The usual operation is a "spike arthrodesis". The patient is given a general anæsthetic. An Esmarch bandage tourniquet is applied to the leg. An ellipse of skin is excised from the dorsal surface of the proximal interphalangeal joint, including the calloused area and underlying bursa. The capsule of the joint is opened, and the lateral ligaments divided. A hole is bored in the base of the middle phalanx. The head of the proximal phalanx is fashioned into a peg to fit the hole. Peg and hole should be about $\frac{1}{2}$ in. in length and in depth. The peg is fitted securely into the hole, and the operation is completed by a few skin sutures. A firm hæmostatic bandage is advisable for forty-eight hours, after which dry dressing and strapping will provide enough splintage. Ankylosis will be firm enough to allow modified walking in an ordinary shoe in ten days, and will be complete in three weeks.

In those cases in which the tip of the toe is flexed, arthrodesis of the distal joint does not prove satisfactory and it is best to amputate the toe through that joint, in addition to fusion of the proximal joint in a corrected position. Amputation of the whole toe is a mistake except in the case of "hammer-toe" consequent on hallux valgus deformity, when the second toe is dislocated. In these cases it is the only method of relieving the painful downward pressure on the second metatarsal head.

NOTES AND QUERIES

Institutional Treatment for Asthma

QUERY.—A lad of twenty is suffering from severe bronchial asthma which has incapacitated him for over a year. There is definitely no evidence of tuberculosis, but I think he should go to a convalescent home or private nursing home, for say, six months, where he can recover in a different environment under medical supervision, if necessary abroad. Would you give me a list of suitable places?

REPLY.—Asthmatics who have been suffering from a prolonged spell of symptoms often do achieve a surprising improvement with residential treatment. Unfortunately in England there is no special institution for the primary purpose of the treatment of asthma. The position is different abroad, however, and in France in particular there are a number of spas which have specialized successfully for many years in the treatment of asthmatics. The best known is Le Mont-Dore in the Auvergne. The late Sir Arthur Hurst, himself a life-long asthmatic, obtained benefit from visits there, a feature of which is the vapour inhalations. Mont-Dore is closed during the winter, and opens in May until September. There are similar establishments at Luchon and La Bourbole in the Pyrenees, both of which are open all the year round. In these spas it is usual for the patient to stay in one of the hotels or chalets, but medical supervision is constant and surprisingly cheap. In Switzerland, asthmatic children often do well at Leysin, at Professor Rollier's Clinic. At Davos, asthmatic patients, both children and adults, are taken at the sanatoria and guest homes, but the position is not entirely satisfactory as the majority of the patients are tuberculous.

NEVILLE SOUTHWELL, M.D., M.R.C.P.

Treatment of Herpes Zoster

QUERY.—I am not at all happy about my ability to control or in any way affect the course of an attack of herpes zoster. In view of the possible development of permanent neuralgia with its pathetic subjective torture I feel that energetic treatment should always be attempted, but can any form other than empirical be offered? I have been in the habit of using anahæmin (B.D.H.) but have not as yet had sufficient experience with it to obtain a genuine idea of its possible efficacy. I would like to know what the best form of treatment may be, and whether it is anything more than empirical? If anahæmin is thought to be satisfactory, in what dosage should it be given and for how long?

REPLY.—Many different substances have been used locally, orally and by injection, in an attempt to cut short the attack of herpes zoster and to minimize the risk of post-herpetic neuralgia. Among these substances are liver extract, posterior pituitary extract and N.A.B. by injection, and the injection of anæsthetic solutions locally. It is, however, quite impossible to determine at the onset which patient is going to have a severe attack or develop neuralgia. All that can be said is that the older the patient the greater the likelihood of the latter occurring. It is therefore equally impossible to assess the value of any therapeutic agent the action of which is unknown, and it is my opinion that the above-mentioned substances play no material part in the control of the course of the disease. Recently it has been claimed that nicotinic acid, in daily doses up to 200 mg., may control the pain, and this substance is certainly worthy of trial.

DAVID KENDALL, D.M., M.R.C.P.

Recurrent Pain in the Thigh

QUERY.—A woman patient, aged sixty, complains of infrequent attacks of severe pain which seems to be referred to the course of the femoral artery in one thigh only. The pain is described as sudden in onset, lasting a few minutes, deeply situated, and quite severe. It is described as being definitely different from a cramp, and during an attack when I was present there was no obvious muscle spasm. The attacks occur without warning, usually while the patient is sitting at rest. The rate of occurrence has been only once in three or four months during the past few years. There are no concomitant symptoms. Apart from some obesity and a past history of cholelithiasis (the gall-bladder being now presumed fibrotic) the patient is healthy. Can you suggest a diagnosis?

REPLY.—The nature of the pain is probably a neuralgia of the anterior crural nerve. An arterial source of the pain can almost certainly be excluded. Some toxic factor is the most likely cause and the gall-bladder should not be excluded by mere presumption that it has become "fibrotic".

LORD HORDER, G.C.V.O., M.D., F.R.C.P.

The Placenta and Lactation

QUERY.—Has the placenta been fully analysed, and are all the components known? Which hormones have been isolated, and in what proportions? I tender this query because so many women have difficulty in producing milk during

death rate from neonatal asphyxia should be sought by improvement in the nutrition and general health of the mothers, early diagnosis and treatment of toxæmia and, when possible, the avoidance of prolonged labour.

The classical division into asphyxia livida and asphyxia pallida is convenient, and emphasizes the greater severity of the latter, which is, however, merely a severe degree of asphyxia with circulatory failure and general collapse. Treatment in any case consists in removing any obstruction to the airway, increasing the supply of oxygen to the brain, and restoring the general circulation.

The infant should be received into a warm sterile towel; there is in general no advantage in allowing the cord to cease pulsating before dividing it, and it is usually more convenient to cut it early and remove the infant to a cot or other prepared place, where it should be placed head downwards on a gentle slope. Mucus and similar material should be cleared very gently from the mouth and pharynx with a swab and a rubber-tipped mucus-extractor; if this can be done before the child takes its first gasp, the risk of aspiration into the finer air passages is reduced. Gentle stimulation, such as rubbing or pinching the skin may be attempted, but more vigorous methods of stimulation are liable to do more harm than good, especially in those feeble infants who are most in need of help.

Oxygen should be given as soon as possible, by soft rubber catheter, by funnel, or in an oxygen tent. It is now generally agreed that in the first few minutes of life there is already an excess of CO_2 in the blood, and that to give a mixture of CO_2 and oxygen at this stage is unnecessary and may be harmful. Most methods of artificial respiration are either dangerous or require equipment not generally available. Rocking, by Eve's technique, is simple, safe, and at least as effective as any other method: the infant, wrapped in a blanket, is held in the operator's arms, and rocked through some 45° on each side of the horizontal ten to twelve times a minute; oxygen may be given by mask or funnel at the same time.

Stimulants have a limited but definite place in treatment; nikethamide, 0.5 to 1 ml. of 25 per cent. solution, or lobeline, 0.25 to 0.5 ml. of a solution containing 3 mg. in 1 ml., may be given into the umbilical vein or intramuscularly. Unfortunately, no stimulant will act on the respiratory centre unless the latter is receiving a sufficient supply of oxygen and, in general, the more severe the asphyxia, the less the response.

When respiration has begun, the infant should be kept warm, but clothes should not be allowed to restrict respiratory movement. Oxygen may have to be continued for several days, preferably in an oxygen tent if available, as there is evidence that some absorption may occur from the skin and stomach. When there is poor expansion of the lungs, inhalations of 7 per cent. CO_2 in oxygen for a few minutes every hour may help at this stage.

If much amniotic fluid has been aspirated, especially when there has been prolonged labour with foetal distress, it is wise to give small doses of a sulphonamide to guard against infection which can so readily be superimposed on the collapsed and waterlogged lung. In the average infant, 0.125 g. of sulphamezathine, six-hourly for five days, should suffice; with this may be combined 10,000 units of penicillin orally every three hours. A close watch should be kept for relapse in the first few days of life; persistent or frequently recurring cyanosis should arouse suspicion of a congenital cardiac defect, even in the absence of a murmur.

W. A. B. CAMPBELL, M.D., D.C.H.

PRACTICAL NOTES

Infrequent Intramuscular Aqueous Penicillin in Treatment of Pneumonia

THREE recent reports from America indicate that satisfactory control of pneumonia can be obtained by the intramuscular injection of aqueous suspensions of penicillin, either once or twice daily. In a series of 206 cases of lobar pneumonia, P. A. Tumulty and G. Zubrod (*New England Journal of Medicine*, December 30, 1948, 239, 1033) treated 70 patients with 300,000 units of aqueous penicillin intramuscularly twelve-hourly; 69 with 20,000, 40,000 or 80,000 units of aqueous penicillin intramuscularly three-hourly; and 58 with 300,000 units of penicillin in oil and beeswax intramuscularly every twenty-four hours. The patients treated with 300,000 units of penicillin in aqueous solution every twelve hours responded to treatment as well as the others, and it is concluded that "the intramuscular administration of 300,000 units of aqueous penicillin every twelve hours is the treatment of choice for pneumococcal lobar pneumonia". M. Hamburger *et al.* (*Journal of Laboratory and Clinical Medicine*, January 1949, 34, 59) record their findings in 64 unselected cases of pneumonia caused by typed pneumococci, in which treatment consisted of 300,000 or 200,000 units of crystalline penicillin G in distilled water, given intramuscularly twice during the first twenty-four hours, and then once each twenty-four hours for six days or until the temperature was normal for forty-eight hours. The mortality was 6.3 per cent. for the entire series, 15 per cent. for the twenty bacterizemic cases and 2.3 per cent. for the forty-four non-bacterizemic cases. Of the four deaths, three were in patients over eighty. During the two preceding winters in the same hospital the mortality in pneumococcal pneumonia was 12 and 14.6 per cent. respectively. A smaller series of 30 cases of pneumonia were treated by W. Weiss and I. Steinberg (*American Journal of Medical Sciences*, January 1949, 217, 86) with 300,000 units of aqueous penicillin G intramuscularly once a day. Pneumococci were isolated from the sputum in twenty-six of the cases. Their results were: eighteen cases (60 per cent.) responded by crisis within twelve to thirty-six hours of the initiation of treatment; nine (30 per cent.) responded by lysis; one patient, in whom *Streptococcus viridans* was found in the sputum, failed to respond, and two patients died (one aged seventy-six, and the other an alcoholic). It is concluded that the

results were "at least as good as those obtained by smaller doses at more frequent intervals". All three reports stress the practical advantages of infrequent injections of an aqueous solution, and all emphasize that blood levels are not the only guide to treatment with penicillin.

Mattress for Patients with Bowel Fistula

A MATTRESS for use in the treatment of cases of ileostomy or high small intestinal fistula, with excoriation of the surrounding skin, which prove refractory to treatment with aluminium paste or aluminium hydroxide gel, is described by W. S. Dempsey and T. E. Jones (*Surgery*, January 1949, 25, 117). An ordinary inner-spring mattress is used in which an opening 6 inches in diameter is made and lined with rubber sheeting (fig. 1). The mattress is placed

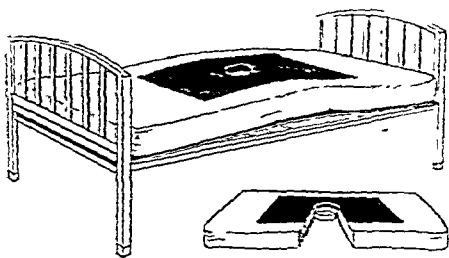


FIG. 1.—Mattress for patients with bowel fistula.

on a hospital bed which breaks in the middle, and the bed is made up with half sheets exposing the opening in the mattress. In this opening a small 6-inch enamel basin is placed, and the patient lies face down on the bed with the fistula directly over the basin. If the fistula is at skin level, side-to-side movement must be voluntarily restricted in order to avoid contact of the drainage with the skin, but if there is a fistula $\frac{1}{2}$ to 2 inches in length, as in the usual ileostomy, it is possible for the patient to roll to either side avoiding contact of the skin with the fistula drainage. Patients of average build are comfortable in this position, but an extremely thin patient may be made more comfortable by breaking the bed slightly in the middle. It is stated that with use of this mattress improvement has taken place within twenty-four to forty-eight hours. A similar mattress may be used in the home for patients with an ileostomy.

the lactational period. Yet most lower mammals, particularly cows, eat their placenta immediately, and as a rule have an abundance of milk. There must surely be some connexion between the ingestion of the placenta and the production of milk.

REPLY.—It is hardly possible to say that *any* tissue or organ has been *fully* analysed, but a number of hormones have been isolated from the human placenta. These comprise œstrogen, progesterone, one or more anterior-pituitary-like gonadotrophins and, possibly, prolactin. The hormone content of the placenta has been reviewed by Newton (*Physiol. Rev.*, 1948, 18, 419). Despite the well-known fact that many lower animals, including herbivorous animals, eat the placenta after parturition, there is no evidence whatsoever that this is essential for, or in any way connected with, the initiation of lactation.

S. J. FOLLEY, D.Sc., Ph.D.

The Pharmacological Actions of Kava

QUERY.—Can you give me any information regarding the pharmacological actions of the kava (*Piper methysticum*) plant in man, particularly the narcotic cerebral effects of the plant, which is used in its native habitat as an intoxicant, and is known to have powerful euphorogenic properties?

REPLY.—In "Drugs, their Use and Abuse", Lewin gives much entertaining information about the use and abuse of kava by South Sea Islanders as a convivial intoxicant. He considers it less harmful than the alcohol which has tended to replace it. The United States Dispensatory (1947) gives references to more modern work, and it is apparent that the Western world has taken comparatively little interest in this drug, so that it is difficult to give a satisfactory answer. Substances known as kawain, dihydrokawain, methylstycin, dihydromethylstycin and yangonin have been isolated, and the effects of extracts on dogs have been studied. Kava has been used chiefly in the treatment of chronic inflammations of the urinary tract, on the basis of the theory that it will act as a stimulant and local anæsthetic during excretion by this route. The development of new pharmacological methods seems to open the way for new work on this drug.

PROFESSOR J. H. GADDUM, Sc.D., F.R.S.

Iodine in the Treatment of Cataract

QUERY.—I shall be grateful for information about the treatment of cataract by calcium and other iodides. I have a patient whose early

cataract appears to have been quite stationary for nine years in circumstances in which I should certainly have expected progress. She has regularly been taking iodides internally in small doses for arterial disease throughout this period. I understand the iodide treatment is local (conjunctival or subconjunctival), but presume iodides can diffuse through the blood-aqueous barrier of the oveal tract.

REPLY.—Cataract is an extremely varying condition. In the senile form iodine has been most extensively used both by local application in an ointment and internally. Neither method has shown definite results. Many ophthalmologists believe that cataract is a normal biological phenomenon of senility—comparable with the greying of the hair and as little amenable to treatment. Many also agree with Rochat that the general condition and abnormalities in nutrition are important in the causation of cataract, and treatment by vitamins is much more likely to be of use than iodine. I have used calcium iodide ointment for many years but not in one single case has a cure been obtained, although in some cases a certain amount of delay in ripening of the cataract seems to have taken place. There are no definite figures given by anyone to prove that iodine either retards or cures cataract.

R. LINDSAY-REA, M.D., F.R.C.S.

Vertigo

DR. W. B. ROANTREE, M.D., F.R.C.S.ED. (Chief Medical Officer, Kolar Gold Field, Champion Reefs P.O., S. India) writes:—"In the Notes and Queries in *The Practitioner*, January 1949, 162, 80, I was much interested in the query and reply on the subject of vertigo. In this part of India there is a well-marked and by no means uncommon syndrome of malaise and vertigo, of sudden onset, lasting usually for ten to fourteen days, and without other symptoms or abnormal findings. It appears to be much more common at some times of the year than at others, and I have had several patients complaining of this condition in the course of a morning's out-patient attendance. Furthermore, I have known it attack husband and wife simultaneously. I myself have had it a good many times. It clears up as suddenly as it appears, leaving no sequelæ. Although not having a vestige of proof, I regard it as a "virus" or "epidemic vertigo", and one of many diseases which have not yet found their way into the medical textbooks. Ménière's disease also occurs here and appears to be an entirely separate entity".

PRACTICAL NOTES

Infrequent Intramuscular Aqueous Penicillin in Treatment of Pneumonia

THREE recent reports from America indicate that satisfactory control of pneumonia can be obtained by the intramuscular injection of aqueous suspensions of penicillin, either once or twice daily. In a series of 206 cases of lobar pneumonia, P. A. Tumulty and G. Zubrod (*New England Journal of Medicine*, December 30, 1948, 239, 1033) treated 70 patients with 300,000 units of aqueous penicillin intramuscularly twelve-hourly; 69 with 20,000, 40,000 or 80,000 units of aqueous penicillin intramuscularly three-hourly; and 58 with 300,000 units of penicillin in oil and beeswax intramuscularly every twenty-four hours. The patients treated with 300,000 units of penicillin in aqueous solution every twelve hours responded to treatment as well as the others, and it is concluded that "the intramuscular administration of 300,000 units of aqueous penicillin every twelve hours is the treatment of choice for pneumococcal lobar pneumonia". M. Hamburger *et al.* (*Journal of Laboratory and Clinical Medicine*, January 1949, 34, 59) record their findings in 64 unselected cases of pneumonia caused by typed pneumococci, in which treatment consisted of 300,000 or 200,000 units of crystalline penicillin G in distilled water, given intramuscularly twice during the first twenty-four hours, and then once each twenty-four hours for six days or until the temperature was normal for forty-eight hours. The mortality was 6.3 per cent. for the entire series, 15 per cent. for the twenty bacteriæmic cases and 2.3 per cent. for the forty-four non-bacteriæmic cases. Of the four deaths, three were in patients over eighty. During the two preceding winters in the same hospital the mortality in pneumococcal pneumonia was 12 and 14.6 per cent. respectively. A smaller series of 30 cases of pneumonia were treated by W. Weiss and I. Steinberg (*American Journal of Medical Sciences*, January 1949, 217, 86) with 300,000 units of aqueous penicillin G intramuscularly once a day. Pneumococci were isolated from the sputum in twenty-six of the cases. Their results were: eighteen cases (60 per cent.) responded by crisis within twelve to thirty-six hours of the initiation of treatment; nine (30 per cent.) responded by lysis; one patient, in whom *Streptococcus viridans* was found in the sputum, failed to respond, and two patients died (one aged seventy-six, and the other an alcoholic). It is concluded that the

results were "at least as good as those obtained by smaller doses at more frequent intervals". All three reports stress the practical advantages of infrequent injections of an aqueous solution, and all emphasize that blood levels are not the only guide to treatment with penicillin.

Mattress for Patients with Bowel Fistula

A MATTRESS for use in the treatment of cases of ileostomy or high small intestinal fistula, with excoriation of the surrounding skin, which prove refractory to treatment with aluminium paste or aluminium hydroxide gel, is described by W. S. Dempsey and T. E. Jones (*Surgery*, January 1949, 25, 117). An ordinary inner-spring mattress is used in which an opening 6 inches in diameter is made and lined with rubber sheeting (fig. 1). The mattress is placed

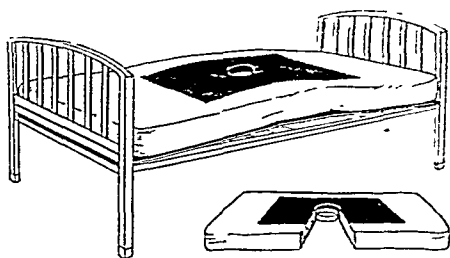


FIG. 1.—Mattress for patients with bowel fistula.

on a hospital bed which breaks in the middle, and the bed is made up with half sheets exposing the opening in the mattress. In this opening a small 6-inch enamel basin is placed, and the patient lies face down on the bed with the fistula directly over the basin. If the fistula is at skin level, side-to-side movement must be voluntarily restricted in order to avoid contact of the drainage with the skin, but if there is a fistula $\frac{1}{2}$ to 2 inches in length, as in the usual ileostomy, it is possible for the patient to roll to either side avoiding contact of the skin with the fistula drainage. Patients of average build are comfortable in this position, but an extremely thin patient may be made more comfortable by breaking the bed slightly in the middle. It is stated that with use of this mattress improvement has taken place within twenty-four to forty-eight hours. A similar mattress may be used in the home for patients with an ileostomy.

Treatment of Allergic Rhinitis

THE intranasal application of pyribenzamine is recommended by J. Brom and J. Zonis (*Journal of Allergy*, January-February 1949, 20, 70) for the treatment of allergic rhinitis. Two or three drops of a 0.5 per cent. buffered solution were instilled into each nostril every three or four hours. After five to seven days it was usually found possible to reduce the instillations to one every twelve or twenty-four hours. The longer the drops were used the better the results and the less frequently had they to be used. In a series of 81 patients there were only five who showed no improvement. Two were unable to tolerate the treatment: one because it aggravated the symptoms, the other because the drops caused "pain in the head". Drowsiness did not occur in any of the patients. In those with accompanying bronchial asthma there was no relief of the asthma. One of the advantages claimed for this form of treatment is the absence of the drowsiness which is so liable to occur with oral administration. An attempt to use a 2 per cent. solution had to be discarded because it caused local irritation. It is pointed out that the local effect is only temporary and that "the usual allergic diagnostic and therapeutic measures are necessary".

Antihistamine Drugs in the Treatment of the Common Cold

THE results obtained with the use of antihistamine drugs in the treatment of the common cold in 572 patients are reported by J. M. Brewster (*U.S. Naval Medical Bulletin*, January-February 1949, 49, 1). Cases of perennial allergic rhinitis were not included in the investigation. The drugs which were used included pyribenzamine, neo-antergan and benadryl, and the dose was 50 mg. every four hours for three doses—or longer if the symptoms persisted. A control series of 72 patients was treated with 16 mg. each of codeine sulphate and papaverine hydrochloride four-hourly. The results in those treated with antihistamine drugs are summarized as follows: Of 21 patients in whom treatment was begun within the first hour of the onset of symptoms, 19 (90 per cent.) were "cured", as were 48 of 55 patients (i.e. 87 per cent.) who were treated within two hours of the onset of symptoms. A similar result was obtained in 116 of 156 patients (i.e. 74 per cent.) treated within six hours of the onset of symptoms, and in 165 of 234 (i.e. 70 per cent.) treated within twelve hours. In the control series "cure" was obtained in one of two patients treated within one hour of the onset of symptoms, 5 of 12 (i.e. 42 per cent.) of those treated within six

hours, and in 7 of 22 (i.e. 31 per cent.) of those treated within twelve hours. The only important side-effect with the antihistamine drugs was drowsiness, and this was most marked with benadryl; it scarcely occurred with neo-antergan.

Ointment for the Treatment of Acne Vulgaris

A SULPHUR ointment of good penetrating power and incorporating an active polysulphide for intradermal use in the treatment of acne vulgaris is recommended by M. J. Strauss and H. Sigel (*Connecticut State Medical Journal*, February 1949, 13, 100). The formula is:—

Sulphur	7.5
Sodium mixed alkyl benzene sulphonate	110.0
Antipyrine	54.0
Triethanolamine	100.0
Propylene glycol	168.5
Water	1000 weight parts.

The ointment is massaged into the skin for two minutes: in the morning, after washing with soap and water, the ointment is applied, allowed to stay on for fifteen minutes, and removed with a towel; in the evening the ointment is applied half an hour before bedtime, and is allowed to remain on all night. If severe irritation of the skin occurs the ointment is applied once daily only, or treatment is interrupted for one or two days a week. Of twelve patients who persevered with the treatment for three months, good results were obtained in all but two. Of the entire group of thirty-one patients, good or excellent results were obtained in 83.3 per cent. It is stated that patients in whom a mild desquamation occurred responded better than those in whom this did not occur.

β -Methylcholine Urethane in Post-operative Urinary Retention

THE subcutaneous administration of β -methylcholine urethane in 76 consecutive cases of postoperative urinary retention is recorded by F. K. Garvey, M. C. Bowman and W. L. Alsobrook (*Surgery, Gynecology and Obstetrics*, February 1949, 88, 196). The drug was given in doses of 5 mg. at thirty-minute intervals, for three injections. If the patient voided satisfactorily after any one of the injections the drug was discontinued; if the third injection did not produce voiding, catheterization was resorted to and the drug was repeated as indicated later. The treatment was successful in 60 per cent. of cases, partially successful in 25 per cent., and unsuccessful in 15 per cent. Side-reactions in the form of flushing, sweating, bladder pain and urethral pain occurred—the two former in 80 per cent. of cases and the latter in 92 per cent. All patients who voided successfully after

administration of the drug experienced bladder or urethral pain, or both. The drug proved a useful adjunct to the treatment of postoperative intestinal distension in 35 per cent. of the patients who passed flatus after the injections. Contraindications to the use of the drug include: vesical neck obstructions, asthma, hyperthyroidism, recent intestinal anastomoses, coronary sclerosis or known heart disease, and elderly individuals except cautiously in small doses.

Nicotinamide in Salicylic Acid Intolerance

L. ROQUES (*Presse Médicale*, February 12, 1949, 57, 154) discusses the value of nicotinamide as an adjunct to salicylic acid therapy for combating intolerance to the latter drug. He cites a small series of cases treated by Meneghini and Norza (*Il Progresso Medico*, 1948, 4, 457). The patients, who were under treatment for rheumatism, were given capsules containing 8 g. of sodium salicylate and 8 g. of sodium bicarbonate for periods of fifteen to twenty days, and from the sixth treatment day for ten days 0.4 g. of nicotinamide subcutaneously. Signs of intolerance to sodium salicylate appeared after two or three days' treatment. In all cases benefit accrued from the nicotinamide therapy: gastric upsets, nausea, vomiting, burning eructations and regurgitation disappeared rapidly. Also after treatment the gastric secretions became normal, with lowered acid content.

A Scalp Ointment

AN ointment that has been found useful in seborrheic conditions, Bernier's prurigo, and psoriasis of the scalp (J. A. Myers: *Pharmaceutical Journal*, February 12, 1949, 162, 119) has the following formula:—

Precipitated sulphur	3
Salicylic acid	3
Sodium sulphuricinate	5
Sulphonated Lorol liquid T.A.	10
Cetyl alcohol-tar mixture	4
Glycerin	5
White soft paraffin	20
Cetyl alcohol	25
Distilled water	28

The ointment is stated to be stable, has a velvety texture and rubs easily into the scalp. The scalp is cleansed by washing with warm water which converts the ointment to a detergent foam.

Xylocaine: A New Local Anæsthetic

THE use of a new local anæsthetic, xylocaine, which is not related to novocain or cocaine, is reported by G. Bremer, S. Ekmanner, H. Persson, and N. Strandberg (*British Dental Journal*, December 17, 1948, 85, 278). Although

for short operations xylocaine was found to be effective without epinephrine, a more profound anæsthesia was obtained with the use of a stabilized 2 per cent. solution with epinephrine content of 1:100,000 or 1:80,000. Advantages of the new anæsthetic noted were:— (1) the short time required for it to take effect; (2) absence of side-effects, such as fainting; (3) its value as a surface anæsthetic.

Inoperable Carcinoma

IN an article dealing with the subject of patients dying of cancer, N. A. Spratt (*Medical Press*, February 16, 1949, 221, 187) recommends the use of the "Brompton Hospital Mixture" for the production of euphoria when the patient is unduly depressed. The formula is:—

Cocaine hydrochloride	½ grain (11 mg.)
Morphine hydrochloride	½ grain (16 mg.)
Clarified honey	60 minims (4 ml.)
Gin	120 minims (8 ml.)
Water	to 1 fl. oz. (28.5 ml.)

The mixture can be given to dying patients "as often as required", but it is stressed that in view of the danger of addiction, cocaine should only be administered when it is certain that the patient is beyond hope of recovery.

Fresh Cabbage Juice for Peptic Ulcer

THIRTEEN patients with peptic ulcer were treated by G. Cheney (*California Medicine*, January 1949, 70, 10) with fresh cabbage juice. The average crater healing time was 10.4 days in seven patients with duodenal ulcer, and 7.3 days in six patients with gastric ulcer. At least a litre of fresh cabbage juice was given daily. Only green cabbage was used. Although, in the author's opinion, the rapid healing of these peptic ulcer craters is not adequate proof that cabbage contains an unidentified factor (vitamin U), which apparently plays a specific part in the healing of peptic ulcers, he considers the results in this small series of cases sufficiently encouraging to warrant further study. Up to the present no extract or concentrate containing vitamin U has been developed for clinical trial.

Treatment of Vulvo-Vaginitis

AS a result of her experience with 51 patients with mycotic vulvo-vaginitis, L. Branscomb (*Southern Medical Journal*, 1948, 41, 534) recommends the following jelly as an effective and practical form of treatment:—

Calcium propionate	9.5 per cent.
Sodium propionate	9.5 per cent.
Propionic acid	1.0 per cent.
Glycerin	10.0 per cent.
Bentonite	32.0 per cent.
Water	38.0 per cent.

REVIEWS OF BOOKS

Atlas of Neuropathology. By WM. BLACKWOOD, M.B., F.R.C.S. Ed., T. C. DODDS, F.I.M.L.T., F.I.B.P., F.R.P.S., and J. C. SOMMERVILLE, A.I.M.L.T. Edinburgh: E. & S. Livingstone Ltd., 1948. Pp. xi and 199. Figures 262. Price 35s.

THIS book fulfils its purpose and provides an excellent visual presentation of the changes found in the special pathology of the nervous system for those entering upon its study. It is not intended as an advanced or comprehensive atlas, and deliberate omissions have been made; thus the mechanical effects of tumours are stressed, rather than their rarer histological varieties. The book is extremely well balanced, some 30 pages being devoted to vascular disease as compared with 10 illustrating the gliomas. The normal specimens illustrated beside such disorders as Huntington's chorea and Pick's lobar atrophy make the abnormalities obvious to the student. Its clinical bias, the short case histories and brief descriptive notes make it an ideal book for a rapid revision of neurology by those taking higher medical qualifications, whilst the beautiful production and many coloured illustrations should find it a place on the shelves of both the general physician and the neurologist.

Advances in Pediatrics. Vol. 3. EDITED BY S. Z. LEVINE, A. M. BUTTER, L. EMMETT HOLT, Jun., and A. ASHLEY WEECH. New York and London: Interscience Publishers Ltd., 1948. Pp. ix and 363. Figures 27, plates 22. Price 45s.

THESE "personalized monographs" maintain a high academic distinction joined with sound clinical sense; and the advances recorded are drawn up in a proper perspective in regard to preceding knowledge. The Editorial Board has again found great strength in the contributors. The book contains much of practical value and there is a suitable balance of physical and psychological considerations. Clement Smith discusses recent trends in obstetrics in reference to the newborn, and to the possible influences of analgesics and anaesthetics on neonatal respiration. The significance and therapy of anoxia are clearly elaborated. This chapter is valuable to the obstetrician and the paediatrician. Retrolental fibroplasia and its disastrous ocular consequences, especially in premature babies, are described and will probably stimulate a greater interest in the condition in this country. A learned essay on recent therapeutics of epileptiform seizures by William Lennox will give many

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Modern Trends in Public Health. EDITED BY ARTHUR MASSEY, C.B.E., M.D., D.P.H., D.P.A., London: Butterworth & Co. (Publishers) Ltd., 1948. Pp. xi and 581. Figures 42. Price 50s.

THIS book is a congeries of twenty-three unrelated essays written by as many authors, all members of the medical profession, with varying distinctions as writers, teachers, practitioners and administrators. The editor has selected subjects of lively contemporary interest although of varying importance, ranging in content from up-to-date appreciations of the classical disciplines and themes of public health to expositions of those new ideas about social medicine which are only taking shape in these post-war years and are of interest to all branches of the profession. It is unfortunate that he has neither conceived of them nor arranged them as a symposium, nor has he given them order and value in an introductory essay. The chapters cry out for a philosophical synthesis. Nevertheless they show collectively by illustration how public health has pushed its frontiers from the environmental sciences through preventive and administrative medicine to cultural and political activities which display it as a social science. Although not a textbook it is a mine of information and most of the chapters have valuable lists of references.

Physics and the Surgeon. By H. S. SOUTTAR, D.M., M.Ch., F.R.C.S. Oxford: Blackwell Scientific Publications, 1948. Pp. vii and 60. Figures 41. Price 7s. 6d.

IN this slender volume Mr. Souttar touches upon many aspects of physics in relation to surgery, ranging from the action of the quadriceps in rowing to the nature of short wave diathermy, from the pressure within an

aneurysm to the energy of decay of radium. Perhaps the most valuable section is that devoted to atomic physics, in which are brief but admirably lucid accounts of the cyclotron, the theory of radioactivity, and similar subjects of great topical interest. It is only a pity that these admirable notes are so short. Having been introduced to Planck's hypothesis, the helium nucleus, and the mass spectograph, the reader would like to know more about them.

Techniques in Physiotherapy. EDITED BY F. L. GREENHILL, S.R.N., M.C.S.P., T.H.T. London: Hodder & Stoughton Ltd., 1948. Pp. x and 222. Figures 37. Price 12s. 6d.

THIS excellent book is written primarily for the physiotherapist. It indicates the various types of disease for which physical treatment is advised and also describes in some detail the appropriate medical and orthopaedic treatments. There are special chapters covering the ground of suspension therapy, special exercises and occupational therapy in medicine, but it is rather surprising, especially as Dr. Heald has assisted in the compilation, that no mention is made of the exact amount of current advised in prescribing the direct current or anodal galvanism. Nevertheless, the book can be thoroughly recommended not only to physiotherapists but to general practitioners. The latter might derive great benefit by reading the work and thus be able to give more accurate instructions to the physiotherapist when ordering physical treatment.

Toxoplasmosis: A Clinical, Serological and Histopathological Study with Special Reference to the Eye Manifestations. BY DR. C. D. BINKHORST. Leiden: Stenfert Kroese; London: H. K. Lewis & Co. Ltd., 1948. Pp. x and 163. Figures 32. Price 15s.

THIS monograph is a first-class production. It is a careful and complete review of the literature since this protozoal disease, common in a number of animals and birds, was first recognized in man ten years ago. The forty-nine cases recorded have been identified on the American and European continents. The fact that the author has collected twenty cases in Holland suggests that the disease is less rare than most imagine. It may occur at any age but is most common in early childhood and is usually congenital. The manifestations are protean, although neurological manifestations predominate in childhood. Neuroretinopathy is an almost constant feature and of great diagnostic value. The coloured plates illustrating retinopathy from most of the author's cases are excellent.

NEW EDITIONS

KAYNE, PAGEL AND O'SHAUGHNESSY's *Pulmonary Tuberculosis*, revised and partly rewritten by Walter Pagel, M.D., F. A. H. Simmonds, M.D., D.P.H., N. Macdonald, M.B., M.R.C.P.ED., and L. Fatti, F.R.C.S., in its second edition (Oxford University Press, 63s.). An appendix is devoted to streptomycin and other chemotherapeutic agents. There is an excellent chapter on collapse therapy, and another on preventive measures, which includes a section on BCG vaccination. The new edition is beautifully produced and illustrated.

Recent Advances in Respiratory Tuberculosis, by Frederick Heaf, M.D., F.R.C.P., and N. LLOYD RUSBY, D.M., F.R.C.P., in its fourth edition (J. & A. Churchill Ltd., 21s.) contains a useful chapter on prevention. Other chapters deal with rehabilitation, including the National Scheme, and with the Public Health Services. The importance of environment in the origin and control of tuberculosis is stressed.

IN the preparation of the fifth edition of *Diseases of the Nose and Throat*, by the late Sir St. Clair Thomson, M.D., F.R.C.P., F.R.C.S., and V. E. Negus, M.S., F.R.C.S. (Cassell & Co. Ltd., 70s.), much of the work of revision was accomplished by the chief author before his death in 1943; recent advances and further revision have been the work of his colleague. Penicillin and sulphathiazole in the treatment of diphtheria carriers; advances in radiotherapy; and a new chapter on sinus infection in children are among the new additions to this well-known textbook.

Psychological Medicine, by Desmond Curran, M.B., F.R.C.P., D.P.M., and the late Eric Guttman, M.D., M.R.C.P., in its third edition (E. & S. Livingstone Ltd., 12s. 6d.) contains among the new additions sections on narco-analysis, prefrontal leucotomy, abreaction, and electric shock therapy. The value of occupational therapy in the treatment of mental disease is emphasized.

Diabetic Manual, by Elliott P. Joslin, M.D., sc.D., in its eighth edition (Henry Kimpton, 12s. 6d.). Among new material is a short chapter on the new insulin syringe recommended by the American Diabetes Association. This work on diabetes is so well known, and its authority so widely recognized, that detailed criticism is superfluous. Both the practitioner and his diabetic patients will welcome the new edition.

Failure of the Heart and Circulation, by Terence East, D.M., F.R.C.P., in its second edition (Staples Press Ltd., 8s. 6d.) contains information on cardiac catheterization, the anticoagulant and xanthine drugs, and the low sodium diet for oedema. A section is devoted to sympathectomy.

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THE PRACTITIONER

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NAPP

NOTES AND PREPARATIONS

NEW PREPARATIONS

ACORZA LIQUIDUM, a combination of codeine and papaverine in a flavoured syrup base, has been prepared for the treatment of the common cold in the early stages. It is issued in vials of 23 ml. Literature and samples on application. (Forsters [Pharmaceuticals] Ltd., Seaham, Durham.)

TABLETS OF RUTIN AND ASCORBIC ACID, each containing 60 mg. of rutin and 25 mg. of vitamin C as ascorbic acid, provide for the combined administration of these two substances. They are available in packings of 100, and 1000, the latter for dispensing. (Allen & Hanburys, Ltd., Bethnal Green, London, E.2.)

TUBERCULOSIS

Streptomycin in Tuberculosis.—The Council of the British Tuberculosis Association has issued the following information:—(1) Although streptomycin has been shown to exert a favourable action in some forms of tuberculosis, its use alone is rarely adequate in the treatment of pulmonary tuberculosis. (2) Streptomycin may cause toxic reactions and must therefore be used with caution. (3) The tubercle bacillus may rapidly become accustomed and resistant to the drug. This resistance may prevent the patient receiving the drug from obtaining proper treatment; it increases the risk of spread of infection to others; it may limit effective administration to one course only. Streptomycin, which is now being manufactured in this country and may shortly become more generally available, should thus only be administered by those experienced or trained in its use. The public should be instructed that only a proportion of patients may benefit, and that great harm may be done to patients and to the community by indiscriminate and ill-timed use of the drug. On the other hand, under suitably controlled conditions, streptomycin may prove of the greatest assistance to sufferers from tuberculosis.

NAPT Colonial Scholarships.—Six scholarships for postgraduate study in tuberculosis in this country during 1949 are open to doctors and other medical personnel throughout the British Colonial Empire and the Sudan. Two are available to doctors with qualifications registrable in the United Kingdom (value £120) or who are graduates of Colonial Medical Schools (value £100), and four are open to matrons, nurses, health visitors, or members of Colonial Sanitary Departments (value £80). Allowances to cover lodging and subsistence will be granted from Colonial Government funds. Applications

should be made through Heads of Departments to be forwarded to the Colonial Office by May 1, 1949.

NEW PHARMACEUTICAL FACTORY IN SCOTLAND

ON March 11, 1949, the Secretary of State for Scotland opened the new factory which has been established by Organon Laboratories Ltd., on the Scottish Industrial Estate in Lanarkshire. This well-planned factory is to become the headquarters of all the research work carried out by this Company in Great Britain. The Company will still maintain its London office at Brettenham House, Lancaster Place, London, W.C.2.

PUBLICATIONS

The Nuffield Provincial Hospitals Trust.—This Report on the purpose and activities of the Trust from 1939-48, is available from the offices of the Trust, 12 and 13 Mecklenburgh Square, London, W.C.1.

The Rh Blood Groups and their Clinical Effects, by P. L. Mollison, A. E. Mourant, and R. R. Race (Medical Research Memorandum, No. 19, revised and reprinted) is obtainable from H.M. Stationery Office, price 1s. 6d.

Neonatal Mortality and Morbidity (Reports on Public Health and Medical Subjects, No. 94) is the Report by the Joint Committee of the Royal College of Obstetricians and Gynaecologists and the British Paediatric Association, issued by the Ministry of Health. (H.M. Stationery Office, 1s. 6d.)

Memorandum on Measures for the Control of Mosquito Nuisances in Great Britain (Mem. 238/Med.) contains information on the use of chemical larvicides, repellents, insecticides and mechanical measures for the control of mosquitoes. (H.M. Stationery Office, 9d.)

Rations and Allowances for Diabetics (P.N. 5327), issued by the Ministry of Health, gives the following:—*Meat*—2 extra rations weekly. *Cheese*—12 oz. weekly. *Fats*—12 oz. extra butter/margarine. *Milk*—if prescribed, 7 pints weekly.

Occupation Centres for Mentally Defective Children is published by the National Association for Mental Health, Maurice Craig House, 39 Queen Anne Street, London, W.1, price 9d.

The contents of the May issue, which will contain a symposium on "Venereal Disease", will be found on page lxxiv at the end of the advertisement section,

THE PRACTITIONER

No. 971

MAY, 1949

Volume 162

THE TREATMENT OF SYPHILIS

By V. E. LLOYD, M.C., M.B.

Director of the Venereal Disease Department, Guy's Hospital.

THE treatment of syphilis has undergone considerable adjustment since the demonstration by Mahoney, Arnold and Harris in 1943, that penicillin had a potent antisyphilitic action. The freedom of this antibiotic from unpleasant or dangerous toxic effects rendered it at once a formidable rival to the older remedies. Many cases of early syphilis were treated exclusively with penicillin between 1944 and 1946, and much information has accumulated concerning its effects upon the infective lesions and upon the serological tests.

PENICILLIN THERAPY

Penicillin, even in small dosage, will effect the disappearance of spirochaetes from a chancre within twelve to twenty-four hours, and will heal the moist erosions of the secondary stage in a few days. The progression of ulceration in a chancre becomes quickly arrested and clean granulations soon appear. The chancre heals in about two weeks. But these effects are apt to be only temporary if penicillin has been given in small amounts or spread over a short period.

TABLE I

RESULTS OF HIGH-DOSAGE SHORT-PERIOD PENICILLIN THERAPY IN EARLY SYPHILIS*

Total no. of units of penicillin	Duration of treatment	Failures within first 12 months
5,000,000	3 hours	4 cases; all relapsed
15,000,000	24 hours	66 per cent.
25,000,000	24 hours	35 per cent.
5,000,000	2 days	75 per cent.
3,000,000	3 days	50 per cent.
5,000,000	5 days	50 per cent.
10,000,000	5 days	5 cases; 1 relapsed

* A composite table from the reports of Lloyd-Jones, Allen, and Donaldson (1946); Lourie, *et al.* (1946) Peters, and Barton (1947); and Lourie (1948).

Dosage.—During the last few years an enormous amount of clinical and laboratory work has been done in attempts to determine the most efficient dosage. With an agent which showed an unmistakable and powerful anti-

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PRE-NATAL DIET

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The normal functioning of the reproductive organs during pregnancy depends, among other things, upon an intake of vitamins and minerals.

Medical opinion is gaining ground that an increased quantitative requirement for vitamin B is indicated in late pregnancy and the early puerperium. Its administration during the period before childbirth has resulted in less vomiting and nausea and in marked improvement in the nutritional value of the breast milk. In order to assure the building of the foetal bones *in utero* and a supply of a necessary constituent of the breast secretions, the importance of calcium is also established.

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Dosage.—During the last few years an enormous amount of clinical and laboratory work has been done in attempts to determine the most efficient dosage. With an agent which showed an unmistakable and powerful anti-

syphilitic action when given in small dosage, it was natural to hope that increasing the total dosage would effect a complete eradication of the disease. But therapeutic trials with very large amounts of penicillin (5 to 25 mega units) distributed over a few hours to a few days have proved to be disappointing (table 1).

The work of Mahoney, Arnold and Harris (1943) suggested that the most effective period of treatment with penicillin given by three-hourly injections would be seven to eight days. Widespread trials were undertaken in the United States to establish the dosage most suitable for early syphilis. In preliminary trials a total dosage of 60,000 units and of 300,000 units, spread over seven and a half days, in three-hourly injections, was found to be ineffective. In other trials, total amounts of 600,000 and of 1,200,000 units produced better results. The use of a total of 2,400,000 units proved much more satisfactory and led to the adoption of this total amount, given over seven and a half days, as the treatment for many cases of early syphilis in the United States Armies during the late war. Subsequent observations, however, have revealed that failures occurred in 12 to 15 per cent. of patients within one year. The results given by a total dosage of 4,800,000 and of 9,600,000 units, recently reported by Rider (1948) and Reynolds (1948) show very little improvement (table 2). Longer observation reveals more failures, and according to Moore (1948) the failure rate of penicillin therapy in general at the end of two years' observation is about 25 per cent.—a somewhat formidable figure.

TABLE 2
RESULTS OF PENICILLIN THERAPY OVER 7½ AND 15 DAYS IN EARLY SYPHILIS*

Total no. of units of penicillin	Intervals and duration of treatment	No. of failures within first 12 months
In watery solution		
60,000	3-hourly for 7½ days	62 per cent.
300,000	ditto	42 per cent.
600,000	ditto	26 per cent.
1,200,000	ditto	18 per cent.
2,400,000	ditto	15 per cent.
4,800,000	ditto	15 per cent.
4,800,000	3-hourly for 15 days	15 per cent.
9,600,000	ditto	13 per cent.
In oil-wax		
4,800,000	Once daily for 8 days	16 per cent.
9,600,000	Once daily for 15 days	11 per cent.

* A composite table from the reports of Reynolds (1948), Rider (1948); Heller, Bowman, and Price (1948); Thomas, Landy, and Cooper (1947); "Report of the Committee on Medical Research and the United States Public Health Service" (1946).

The great difficulty of providing hospital in-patient accommodation for the three-hourly injections over seven and a half days led to the introduction of penicillin incorporated in slow-release vehicles, of which beeswax and

arachis oil has proved the most suitable for treatment based on single daily injections in out-patients. The recently introduced procaine penicillin (Herrell *et al.*, 1947), which also is slowly absorbed and which gives a detectable blood content of penicillin for twenty-four hours, should also be efficacious by single daily injection.

COMBINED USE OF PENICILLIN, ARSENIC AND BISMUTH

Although penicillin used alone has a rapid healing action on the lesions of early syphilis, it is clear that observation over a period of one to two years has brought to light a disturbing number of relapses. For this reason the tendency to abandon the older treatment with arsenicals and bismuth, which raised prompt objections by Harrison in 1945, has given way to the use of a combination of the three agents—a judicious blend of the old and the new. However, in spite of the limitations of penicillin, its introduction into the treatment of syphilis has shortened the former long drawn-out period of treatment from twelve to eighteen months to three to six months. This shortening of the treatment period is of great public health value because a far greater proportion of patients now actually complete the planned schedule of treatment.

Excellent results of a combined course of this nature, comprising 3 to 4 mega units of penicillin in the first eight days, together with neoarsphenamine and bismuth injections for a further six weeks, have recently been reported by McElligott, Jefferiss and Willcox (1948). They noted only 4.7 per cent. of failures in the first twelve months of surveillance.

TREATMENT OF PRIMARY AND SECONDARY SYPHILIS

Penicillin therapy should be instituted as soon as a diagnosis of syphilis has been made and should not be begun until that diagnosis is beyond doubt. In hospitals or in nursing homes multiple injections at three-hourly intervals are sometimes practicable, and in this event aqueous sodium penicillin should be given in individual doses of 80,000 units in 60 injections spread over seven and a half days (total 4,800,000 units). Such accommodation, however, is not often available and may be refused by the patient who anticipates difficulty in explaining his presence in hospital to his relatives or friends. The great majority of patients are now treated as out-patients with one of the oil-wax preparations of calcium penicillin, in doses of 600,000 units once a day for eight days (table 3). Penicillin urticaria, which is the only sign of intolerance to penicillin likely to be encountered, is treated with benadryl, in oral doses of 50 mg. t.i.d.

It will be found that many patients experience some difficulty in arranging at short notice for a daily attendance for eight days. The desired arrangement can usually be made for beginning treatment within a few days, and during this interval it is imperative to give an injection of neoarsphenamine

and of bismuth so that the progression of the infection during the waiting period may be prevented.

During the penicillin treatment, 0.3 g. of neoarsphenamine is given intravenously on the third, and 0.45 g. on the seventh day. Later, after the penicillin therapy, 0.6 g. of neoarsphenamine is given once each week for the next seven weeks; a total of 4.95 g. is thus reached. This amount of neoarsphenamine is maximal and should be reduced for a patient whose weight is under ten stone. For patients of particularly light weight the dose suitable is calculated at the rate of 0.004 g. per pound of body weight; thus a patient weighing 6½ stone should be given 0.35 g. as the maximal weekly dose. On completion of the penicillin treatment, and concurrently with the arsenical therapy, bismuth oxychloride in weekly intramuscular injections of 0.2 g. is given for seven weeks; this may be given at the same time as the neoarsphenamine injection or on another day in the same week, but the seven-day interval should be maintained.

TABLE 3

SCHEDULE OF TREATMENT FOR AMBULANT CASES OF PRIMARY, SECONDARY AND EARLY LATENT SYPHILIS

Day				Penicillin in oil-wax or procaine penicillin	Neoarsphenamine	Bismuth oxychloride
				units	grammes	grammes
1st	600,000	—	—
2nd	600,000	—	—
3rd	600,000	0.3	—
4th	600,000	—	—
5th	600,000	—	—
6th	600,000	—	—
7th	600,000	0.45	—
8th	600,000	—	—
12th (2nd week)	—	0.6	0.2
3rd week	—	0.6	0.2
4th week	—	0.6	0.2
5th week	—	0.6	0.2
6th week	—	0.6	0.2
7th week	—	0.6	0.2
8th week	—	0.6	0.2
Total	4,800,000	4.95	1.4

A small number of patients are intolerant to the arsenical compounds. Arsenical dermatitis, the most frequent complication, should be suspected whenever any irritating erythematous or papular rash appears during treatment. Treatment is with BAL (dimercaptopropanol) by injections of 2 ml. of a 5 per cent. solution in oil with 10 per cent. benzyl benzoate six-hourly on the first day, and twice daily for three or four more days. Toxic effects, such as acute encephalopathy, agranulocytosis, and aplastic anæmia, are rare but have a high mortality. BAL is reported to be of some value in these complications.

During this schedule of treatment the infectivity of the primary chancre and of the secondary rash is rapidly controlled and the lesions heal within a few weeks. When the Wassermann reaction is negative at the beginning of treatment it usually remains negative during and after treatment. In the positive cases there is gradual decrease in the intensity of the reaction until it becomes negative within three to four months. The persistence of a positive result into the fifth or sixth month should be interpreted as being a failure to cure the infection, and an additional similar course of treatment is advisable. A positive result ensuing after a previously negative result should be taken as portending a relapse, and re-treatment is recommended.

Relapse after penicillin therapy alone appears to occur most often in the third or fourth month. It is not unlikely that such relapses may be forestalled by giving another eight-day course of penicillin at the end of the second month of treatment, immediately after the last injection of neoarsphenamine. A schedule of treatment of this nature, i.e., eight days penicillin, eight weeks neoarsphenamine and bismuth, eight days penicillin, is on trial at present in the venereal disease department of Guy's Hospital.

Treatment during pregnancy.—The treatment of the pregnant syphilitic woman should be along the lines indicated for early syphilis, but for the patient who first comes under medical care late in her pregnancy there may be insufficient time to complete the whole of the combined treatment. In this event she should receive an eight-day course of penicillin followed by as many of the injections of arsenic and bismuth as can be arranged, and a second course of penicillin near the end of pregnancy. In the prevention of congenital infection of the child by treatment of the infected mother during her pregnancy, penicillin therapy has given strikingly successful results (Ingraham *et al.*, 1946; Goodwin and Moore, 1946).

Local treatment for small clean chancres is not necessary as they heal rapidly under systemic treatment. For a large ulcerated chancre, local bathing with hydrogen peroxide followed by the application of penicillin cream is useful. Foul sloughing ulcers respond to treatment with flowers of sulphur after soaking in hydrogen peroxide. Impending phagedæna may require a dorsal incision of the prepuce to provide adequate drainage.

A soft sore (chancroid) may simulate a syphilitic chancre. It does not heal with penicillin or arsenical treatment, but will respond to oral sulphonamide therapy. A syphilitic chancre erroneously treated as a soft sore with a sulphonamide will not heal and spirochaetes can be found in spite of the sulphonamide treatment. Penicillin injections or penicillin cream locally should never be used for a genital sore of unknown etiology until syphilis is excluded.

SURVEILLANCE AFTER TREATMENT AND TESTS OF CURE

The uncertainty of the outcome of treatment in early syphilis indicated by the proportion, small though it may be, of failures or relapses renders it

imperative for every patient to remain under clinical and serological observation for some years. The ideal period is for the remainder of the patient's lifetime, but this is rarely, if ever, practicable. Every patient after full treatment should be kept under clinical and serological observation at regular intervals for a period of at least three years. Serological tests and a clinical examination should be done at monthly intervals during the first three months, at three-monthly intervals during the next year, and for another two years at intervals of six months. In order to detect the presence of asymptomatic neurosyphilis, the cerebrospinal fluid should be examined at the end of the first year after treatment. A presumptive cure may be entertained when, at the end of the three years' period of surveillance in a case of early syphilis, which has been fully treated, all clinical and serological observations have shown no evidence of the disease.

TREATMENT OF TERTIARY SYPHILIS

In general, the routine treatment applicable to the young adult suffering from syphilis in its early stages is rarely suitable for patients with tertiary syphilis, chiefly because the infection is of long duration, but also on account of the destructive quality of tertiary ulceration, the nature of the structures involved and the presence of other diseases. In contrast to early syphilis, the treatment of tertiary syphilis is essentially that of the individual patient and his lesion rather than that of the infection.

The aims of treatment in these late cases are to prevent further extension of the disease, to attain resolution of the lesions, and to restore the damaged structures so far as is possible. In planning and managing treatment the general condition of the patient, and in particular the state of the heart, liver, lungs and kidneys, must be considered. In elderly patients much harm to the general health may be caused by injudiciously intensive treatment, particularly with the arsenical compounds, at a time when complete eradication of syphilis is impossible. In general, the treatment should be mild and leisurely.

Latent syphilis.—In the management of syphilis in the middle-aged and elderly patient a frequent problem is that of the treatment of "latent" syphilis. It is customary to use this term for those cases of torpid syphilis, some with a history of syphilitic infection and some without, in which no signs of the disease can be detected by thorough examination but in which positive serological tests for syphilis are repeatedly obtained. Latent syphilis should never be diagnosed on the result of a single serological test because laboratory errors in technique or recording are not unknown, and biologically false positive results are sometimes met with in association with conditions other than syphilis. Confirmatory tests with the Wassermann and Kahn reactions must be obtained. The so-called provocative action of an injection of a neoarsphenamine compound on serological tests is no longer considered of value.

The diagnosis of latent syphilis is one that is arrived at slowly and carefully by elimination and should not be made without X-ray examination of the heart and aorta to eliminate asymptomatic aortitis, and full tests of the cerebrospinal fluid to eliminate asymptomatic neurosyphilis.

The treatment of latent syphilis, however well the patient may appear, is regarded as being necessary to prevent the development of tertiary lesions, particularly of vital structures, in the future. It should not be forgotten that many patients with tertiary syphilis can give a long history of latency, nor that the woman with latent syphilis is a well-known producer of infected children.

The type of treatment advised depends to a great extent upon the age of the patient and upon an estimate of the duration of the infection; but often there is no recollection by the patient of the time of infection. When it becomes clear or probable from the history that syphilis was acquired less than ten years previously the case should be treated according to the schedule of treatment recommended for cases of early syphilis; but this should be preceded by potassium iodide, 30 grains (2 g.) daily, together with weekly injections of bismuth oxychloride for a month. The positive serological tests are usually reversed very slowly by treatment, and several such courses, with intervals of six weeks, may be required. In some cases the serological tests remain obstinately positive in spite of prolonged treatment, but it is thought that treatment over twelve to eighteen months will be sufficient to perpetuate the latency and to prevent any later disasters. The attainment of a negative serological test within three to six months suggests that the infection has been present for a year or two only; nevertheless, at least two full courses of treatment should be given.

Tertiary syphilitic lesions.—Lesions of the skeletal structures—skin, mucous membranes, bone, muscle—are of slow formation and relatively benign in nature. The general health of the patient is but little affected, although, over a long period of time, the extent of local tissue destruction may be considerable. These gummatous nodules or ulcers respond readily, even to mild treatment. Resolution can be effected by potassium iodide, 30 grains (2 g.) daily, but is more speedy when a bismuth compound is given at weekly intervals. Penicillin is very efficacious; cutaneous ulcers heal rapidly when 250,000 units of penicillin in oil-wax are given only once a week. In aged patients there is no necessity for more intensive treatment. For those aged fifty-five years or more, penicillin in oil-wax or procaine penicillin is injected twice a week in doses of 300,000 units, together with potassium iodide orally, 20 grains (1.3 g.) t.i.d., for four weeks. For particularly slow healing ulcers of the skin, additional treatment with bismuth oxychloride, in doses of 0.1 g. once a week, should be given over eight weeks. Tertiary ulceration of the face around the nasal orifices and mouth is apt to be more progressive than elsewhere. Ulcers or gummas of the palate and nasopharynx are also often rapidly destructive. The amount of tissue

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are not advised. After an interval of a month another similar course, beginning with the penicillin, should be given. Ultimate resolution of the gummas is sometimes very slow and even after a year or two some further improvement may take place; in these protracted cases additional treatment is advisable.

CONCLUSION

In spite of the disappointment in the hope of penicillin becoming the sole agent required for the treatment of syphilis, and thereby superseding the older and more toxic compounds, this antibiotic has nevertheless taken a permanent and important place in the treatment of syphilis in all its stages and manifestations. Its introduction has shortened considerably the period of treatment of the early stages, with great advantage to the individual patient and to the community. In the prevention of congenital syphilis by treatment of the pregnant syphilitic woman it is a noteworthy advance. In the later manifestations also, penicillin is of high value and of inestimable worth when age or ill-health precludes the employment of any of the arsenical compounds.

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destroyed and later to be cast off as a slough is invariably greater than surface appearances suggest. This is particularly so in the soft palate. For these lesions full treatment is urgently needed. Iodides, daily penicillin and bismuth should be begun promptly and continued in an attempt to prevent gross tissue destruction.

In these elderly cases, as in all cases, pyorrhœa or dental caries—frequent precursors of bismuth stomatitis—should be attended to before bismuth therapy is undertaken; there is no risk of this complication in the edentulous patient. Organic arsenical compounds are not advised for the elderly patient. The positive serological reaction will usually remain unaltered by treatment and should not be taken as a guide to progress or further treatment; in fact, further tests are best omitted.

In patients under the age of fifty-five with tertiary cutaneous syphilides, or with latent syphilis, there is possibility of the future development of cardiovascular or neurological syphilis. Rigorous clinical examination, together with X-ray examination of the heart and aorta, and full tests of the cerebrospinal fluid, should be done before treatment is begun. Preliminary treatment is with potassium iodide, 30 grains (2 g.) daily, and intramuscular injections of bismuth oxychloride, 0.2 g. once each week, for four weeks. This should be followed by penicillin in oil-wax, or procaine penicillin, in daily injection of 600,000 units, for eight days. After this, weekly injections of neoarsphenamine, beginning with 0.3 g. and increasing to 0.6 g., are given for eight weeks. Finally, four additional weekly injections of the bismuth are given. After an interval of four weeks a second similar course should be given. When the patient's general health is not good the neoarsphenamine may be replaced by acetylarsan, by intramuscular injection in doses of 3 to 5 ml. once a week.

Syphilitic disease of bone is considerably slower to resolve than lesions of the skin. Although symptomatic relief may be obtained in a few weeks, many months of treatment may be required before the bony disease is arrested.

Syphilis of the liver.—The effect of antisyphilitic treatment in cases of gummatous liver is usually highly gratifying. Pain and tenderness cease in a few weeks, there is marked improvement in the patient's general condition and an appreciable decrease in the size of the liver. In advanced cases with ascites, specific therapy is of doubtful value. On account of the natural tendency of the gummatous tissue to contract and distort the liver, often culminating in obstruction to the portal vein or the bile duct, specific therapy should be applied very gently and is best initiated with iodides.

For the first two weeks, potassium iodide, 10 grains (0.65 g.) t.i.d., is advised. Subsequently, penicillin is given twice weekly in doses of 200,000 units for four weeks. For the next six months steady treatment with potassium iodide, 20 grains (1.3 g.) t.i.d., and with injections of bismuth oxychloride, 0.1 g. once a fortnight, is recommended. The arsphenamines

There followed a series of studies designed to portray the shortest time-interval which would be required for an excessive amount of penicillin to combat early syphilitic infections. Of outstanding interest was the finding that a schedule employing 200,000 units administered at two-hour intervals for a total of 36 injections produced a pattern of cure comparable to that of the seven-day schedule. A series in which the treatment period was further reduced to forty-eight hours failed to reveal cure rates comparable to the seven- and three-day schedules.

During this period the pharmaceutical manufacturers were experimenting with vehicles which delayed the absorption of the antibiotic and obviated the use of frequent injections. The initial product in peanut oil and beeswax (P.O.B.) became known as the Romansky formula. More recently, a preparation of *procaine penicillin in oil* with 2 per cent. aluminium monostearate has been made available. Early experience with this product points to the possibility of further simplifying the treatment of syphilis.

It was found that 600,000 units of this procaine penicillin preparation, given at intervals of twenty-four hours for a total of three injections, was capable of producing demonstrable levels in the blood for as long as seven days. On the basis of this information, a series of 100 patients with early syphilis was treated with the above routine. The results in over-all cure rates are comparable to those obtained in the seven- and three-day schedules. The findings, if confirmed by more prolonged observation, suggest that the future therapy of the disease may involve as few as three injections of penicillin and a treatment period of not more than forty-eight hours.

At no time during the penicillin era has evidence been presented indicating that the results of the therapy of early syphilis would be enhanced through the addition of arsenic, with its inevitable hazard of severe toxicity, or of bismuth.

RELAPSE RATE

The medical men who treated syphilis before the advent of antibiotic therapy all probably have a healthy respect for the ability of the disease in some instances to remain active and destructive over a period of years, even in the face of therapy. This respect has given rise to a spirit of caution which is responsible for a reticence to give expression to some of the features which are slowly becoming apparent.

As experience with adequate penicillin therapy encompasses an increasing number of patients observed over a lengthening period of time, an impressive fact is the practical absence of central nervous system manifestations among patients treated in the early stages of the illness and observed closely by the group responsible for the original diagnosis and treatment. It is realized that the lapse of time exceeds five years in only a very small group of patients. However, unless this type of relapse is observed in the reasonably near future, the conclusion will be entirely warranted that this severe complication of syphilis can be prevented by adequate therapy in the early stages of the infection.

THE TREATMENT OF SYPHILIS IN THE UNITED STATES

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IN the midst of so definite a change in the relationship of a disease to its human host as is now being experienced in syphilis, it becomes more than difficult to speak with any degree of accuracy as to the thought and opinion of the medical profession of a country. No attempt will be made to present a canvas of the older concepts of syphilotherapy or the extent to which they are observed to-day; instead, an effort will be made to show the advances in the antibiotic therapy of syphilis which have already occurred or which are in the formative stage.

ANTIBIOTIC THERAPY

Antibiotic therapy was introduced in 1943. *Penicillin* was the first of this new type of substance to be employed in syphilotherapy. The capacity of the antibiotic to destroy the spirochæte of syphilis was readily demonstrated, first in the rabbit, then in man. There followed a series of guided studies designed to portray the optimal time-dose relationship for the treatment of early syphilis. The results of many of these studies have been published. From this point forward the present review will represent my views on the subject, all of which can be supported by the data produced in carefully conducted studies. Whether or not all workers in the field are in general accord with these views will not enter into this presentation.

The treatment routine employed in the group of patients who formed the basis of the original report on the subject of penicillin therapy, consisted of 1.2 mega units of amorphous penicillin, administered intramuscularly in 25,000-unit amounts at four-hour intervals, for a total of 48 injections. This schedule was an entirely arbitrary selection, but subsequent studies show that the original schedule represents a close approximation of the time-dose relationship which appears to offer the best prospects for successful treatment.

The second experimental schedule employed 2.4 mega units of penicillin, administered at three-hour intervals; the third employed 1.7 mega units, but with a reduction of the time-interval to two hours. Probably the most satisfactory of the early treatment schedules was the one utilizing 3.4 mega units of penicillin, administered by intramuscular injections of 40,000 units at two-hour intervals for a total of 85 injections. The re-treatment rate for the 728 patients treated by this schedule approximated 4 per cent. This included reinfections which could not be differentiated (nor can be at present) from clinical relapses.

THE TREATMENT OF NEUROSYPHILIS

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THE treatment of neurosyphilis is at the present time dominated by penicillin, and even those who continue to use some malaria for general paralysis agree that the introduction of penicillin has otherwise revolutionized therapy. The discovery that penicillin had a beneficial effect on general paralysis and other forms of neurosyphilis was certainly a surprise, because penicillin was introduced as an antibacterial remedy, and previous experience of such remedies had not led to the expectation that it would have any beneficial effect on a spirochætal infection. The surprise did not end there, because it had already been discovered that penicillin given intramuscularly did not find its way into the cerebrospinal fluid, and if it did not pass the blood-brain barrier it could not be expected to be effective in general paralysis and other forms of parenchymatous infection of the nervous system. Practical experience has, however, confounded the theoretical objections, and although there are still many who have not sufficient confidence to dispense with malaria entirely, all are agreed that for every form of neurosyphilis penicillin is a very potent remedy.

It is important that anyone who undertakes the management of a case of neurosyphilis should have clearly in mind both the possibilities and the limitations of treatment, and not all of those who have tried to make comparison between the newer and the older methods of treatment have shown a clear grasp of the limitations. All that can be expected from treatment, whether chemical or biological, in the present state of knowledge, is the extermination of the syphilitic infection; symptomatic improvement thereafter depends upon the recovery of the nervous tissue, a process which we have as yet little or no power to influence. Even if the patient on entering the hospital were to pass through a magic ray which killed off every spirochæte in his system, there would be no immediate change in his symptoms, since these depend upon disturbances of function of his nervous tissues; and recovery of the nervous tissues, so far as they will recover, requires time. Improvement will go on in many instances for two years or more after successful treatment, and the degree of clinical recovery that will eventually occur depends upon the extent to which the nervous tissues are capable of recovering.

SIGNS OF SUCCESSFUL THERAPY

Since there is as yet no means of influencing this process of recovery of the nervous tissues, it must be left to look after itself while efforts are directed to the eradication of the infection and an endeavour to obtain the arrest of

An old axiom in syphilotherapy postulated that a patient having contracted the disease could not be considered cured without undergoing a period of observation extending into one or two decades. It is becoming increasingly evident that treatment failures, either serological or clinical, are detectable within the initial nine months of post-treatment observation and that, having passed that period, the great majority of patients tend to progress towards sero-negativity.

THE VALUE OF SEROLOGICAL TESTS

A word in regard to the future rôle of the blood test may be timely. In antibiotic therapy the serological curve in the post-treatment period becomes of maximum importance. After the disappearance of the clinical symptoms, the behaviour of the serological curve forms the only available index to the progress of the therapy. This requires that the physician be supplied with a quantitative estimate of the concentration of the reacting substance in the blood serum. The previously acceptable methods of reporting test findings involving the terms "positive" and "doubtful", or the use of numerals from 1 to 4, will be found entirely valueless in the management of the early syphilitic patient treated with penicillin.

Another and more serious aspect of the future therapy of syphilis is in prospect. If the treatment of the disease continues its trend towards simplicity and the therapeutic agent continues to be without harmful side-effects, it may become expedient to treat the patient rather than to be guided by laboratory procedures which may or may not lead to the correct diagnosis. In gonorrhœa it is at present simpler to rely upon a single injection of penicillin than to attempt a diagnosis through the identification of the *N. gonorrhœæ* by culture methods. The relationship of serology to the diagnosis of syphilis may undergo a similar change.

CONCLUSION

From the public health standpoint the development of antibiotic therapy may have far-reaching results. In penicillin there has been made available a non-toxic agent which has the undoubted capacity for bringing the infective stages of the disease to a speedy termination. If to this capacity is added a search for, and elimination of, sources of infection, and close observation (or even prophylactic treatment) of individuals exposed to known infective sources, then a decline in the prevalence of the disease may be expected.

The eventuality to be most feared is the development of a resistance to penicillin by the syphilis spirochæte. Up to the present no instances of this kind have been encountered in my experience. However, such an occurrence is well within the range of possibility and could cause the undoing of much of the work of the past five years. This has stimulated the search for new antibiotics capable of replacing penicillin in the event of loss of its effectiveness. The demonstration of the spirochæticidal capacity of aureomycin is a step in this direction.

in the fluid is the colloidal gold (Lange) curve, and this may remain positive, although gradually weakening for a year or two, or even more, in a fluid which has become otherwise quite normal. The significance of this persistence is difficult to assess, but the important thing for the clinician to know is that it does not indicate any persistence of syphilitic infection. If the cerebrospinal fluid becomes normal, it can be assumed that the syphilitic infection of the nervous system has been exterminated. The Wassermann and other reactions may, however, remain strongly positive in the blood, and the significance of their persistence is at present difficult to estimate. This is discussed by Orpwood Price (p. 377).

The objective of treatment, then, is the eradication of infection from the nervous system, and the criterion of success is the return of the cerebrospinal fluid to an "inactive" state and its final restoration to normal. If that objective is attained, clinical improvement will follow up to the limits of recoverability of the nervous tissues.

GENERAL PARALYSIS OF THE INSANE

Since penicillin became available in the Spring of 1945, I have used no malaria or other pyrexial therapy. In January 1948, I reported the results of treatment in a small group of 24 cases of different types of neurosyphilis, including 8 cases in which there were mental changes and "paretic" abnormalities in the cerebrospinal fluid. All the patients had been followed up for at least a year, and some for as long as three years. In all of these instances the cerebrospinal fluid had become normal after treatment of the patient with penicillin, except that in a number of cases the colloidal gold curve was still more or less positive. These cases have now been reviewed after another year and in none of them does either the clinical state or the state of the cerebrospinal fluid give any indication of recrudescence of the syphilitic infection. The following cerebrospinal fluid findings may be taken as a typical example (table 1). The patient received eight million units of penicillin divided into two courses of four million each (although now it seems that the second course may have been unnecessary and may in fact have excited a slight cellular reaction).

TABLE 1

	Cells per c.mm.	Protein mg.	Globulin N.A.Pandy		W.R.	Lange
Before treatment						
→ million units ..	38	80	+	—	4444	4544322100
After treatment						
1-2 weeks ..	16	80	+	—	4322	3443210000
7 months ..	3	60	+	—	4200	4433211000
→ 4 million units						
8 months ..	3	55	+	+	neg.	4554321100
12 months ..	6	40	—	+	neg.	2233321100
24 months ..	1	40	—	—	neg.	0000000000

the inflammatory process by the safest means and as promptly as possible. How then are we to know that the infective process has been arrested and that the infection has been eradicated? Whatever method of treatment is employed the only criterion is the return of the cerebrospinal fluid to a condition which gives no evidence of inflammatory activity, and its persistence in such a state. The presence of syphilitic activity in the nervous parenchyma or meninges is revealed by an excess of lymphocytes (and sometimes a few cells of other kinds) in the cerebrospinal fluid and, whatever other changes are present in the fluid, the first sign of the abolition of active inflammation is the restoration of the cell count to normal. Within a few weeks of successful treatment the quantity of cells in the fluid will be three or at most four per c.mm., and greater confidence will be felt if the number is nought or one.

Alajouanine has recently introduced a technique for obtaining fluid from around the cerebrum, and insists that the number of cells in this fluid must be restored to normal before the absence of all spirochætal activity can be assumed. The cerebral fluid is obtained by lumbar puncture after withdrawal of about four successive specimens of 10 ml. each of spinal fluid and their replacement by air; in this way all the fluid from the spinal theca is removed and fluid from the cranial cavity is obtained. A fluid in which the number of cells is normal, whatever other changes may still be present in it, is described as an "inactive" fluid and Dattner (1944), as the result of a long experience, emphasizes that a really "inactive" fluid never becomes active again, and in consequence, if the fluid has reached a reliably inactive state, it is justifiable to be confident that the infective process has been abolished.

The other changes that occur in the cerebrospinal fluid after successful treatment are slower, and it is essential that they should be known in order that the importance of their presence can be properly assessed. In many syphilitic conditions the amount of protein in the fluid is increased and a year or more may be required after successful treatment before this returns to a normal level. In fact, with the excretion of waste products as inflammation subsides, the amount of protein may rise (as it does in other inflammatory diseases) and later show a gradual reversion to normal.

In a recent case of general paralysis the amount of protein in the fluid before treatment was 90 mg. per cent.; eight days after the conclusion of a course of penicillin it had risen to 120 mg. per cent.; by the end of two months it had fallen to 100 mg. per cent.; and after ten months was 40 mg. per cent., which is within normal limits.

The tests for excess globulin usually become normal about the same time as the total protein. The Wassermann reaction in cases of general paralysis and other parenchymatous syphilis is strongly positive in the spinal fluid and may remain positive for a long time after the cell count and clinical improvement have indicated the cessation of syphilitic activity. In nearly all cases, however, it has become negative in the spinal fluid by the end of a year after successful treatment. In general, the Wassermann reaction in the fluid seems to die out more quickly after treatment with penicillin than after treatment with malaria. The most persistent of the abnormal features

produced when compared with the first year or two of penicillin responses; but penicillin rapidly overtakes malaria in the second and equals it in the third year of the observation. Taking the durability of penicillin effect . . . the comparative simplicity, short duration, and safety of penicillin therapy into account, it begins to look as if penicillin alone were the equal of malaria in paresis . . . Spinal fluid results . . . are apparently superior with penicillin to those obtained with malaria . . . In tabo-paresis the fluid improvement with penicillin definitely surpasses that obtained with malaria, and the symptomatic improvement with penicillin is equal after the second year: in meningovascular neurosyphilis the results are markedly superior serologically and equal clinically . . ."

Penicillin versus malaria.—There are many physicians who have as yet insufficient confidence in penicillin therapy and, impressed with the apparent intensiveness of malarial treatment, use an abbreviated course of malaria, hoping thereby to reinforce the effects of penicillin. The clinical improvement obtained with the initial penicillin therapy renders the patient better able to withstand the malaria. It is therefore necessary to consider whether or not any better results can be expected by giving malaria as well, and whether the supposed additional advantages are commensurate with the risk involved. The questions may perhaps be answered in two ways:—

(1) Practical experience of comparable series of cases treated with penicillin, with and without malaria, seems to indicate that there is no great difference in the results when malaria is added. In a series described by Rose and Solomon (1947) there was no material difference in the percentages of clinical improvement whether the patients were treated with penicillin and malaria, penicillin and the fever cabinet, or penicillin alone. From the report of a small series described by Lescher and Richards (1947) in this country it is also evident that the results were very similar, although these observers concluded that the best clinical results seemed to be achieved with penicillin and malaria closely followed by those obtained with penicillin alone.

(2) Considering the matter theoretically:—If a rapid arrest of the syphilitic process can be obtained by any means, additional treatment for the same purpose is useless, and if it involves risk, it is certainly unjustified. Everything seems to indicate that the syphilitic processes are inhibited by penicillin before malaria would even have passed through its incubation stage. Moreover, although penicillin therapy lacks the respectable age of malarial therapy and cannot yet point to long-sustained cures, there is now much serological evidence that penicillin is the more effective of the two treatments, and if so, giving malaria as well is an attempt to reinforce the stronger by the weaker.

Neither the practical results recorded nor theoretical considerations lead me therefore to believe that anything is gained by giving malaria as well, provided that the dosage of penicillin is adequate. After any effective treatment the extent of clinical recovery depends upon the amount of cerebral tissue that is capable of recovery; this is independent of the nature

Penicillin therapy.—Experience in this country and in America has shown that a total of about 5 million Oxford Units is required for the successful treatment of a case of general paralysis, and the tendency is to give 6 or 8 million units. It has been customary, in order to maintain a sufficient concentration of penicillin in the blood, to give injections every three hours, and after the first day to give a total of approximately half a million units each day. Various methods are now on trial of maintaining adequate concentration of penicillin in the blood with a smaller number of injections, and in some clinics it is the practice to give one million units daily in one or two injections; and others are experimenting with the combinations of penicillin with wax or oil. For the first day of treatment the doses given are small as a precaution against Jarisch-Herxheimer reactions. They may be either of the order of 15,000 units three times in the course of the day, or 10,000 units hourly, with instructions to the sister to stop administration if the patient seems upset or makes any complaint. Personally, I have observed no untoward reaction of any kind. In all cases penicillin has been given by the intramuscular route only; intrathecal administration is unnecessary and is apt to excite harmful reactions.

Results of treatment.—In my experience the clinical and serological results of such treatment are at least as good as those formerly obtained with malaria. It must be recalled that the mortality associated with the period of malarial treatment and the subsequent months is 8 to 10 per cent. With penicillin treatment nearly all of this mortality is avoided, but instances have been recorded in which penicillin has failed to save the patients in some cases of fulminating general paralysis of the insane. Malaria alone effectively arrests the disease in 55 to 60 per cent. of the cases of general paralysis, and among the remainder the mortality in subsequent years is heavy, so that 40 per cent. of all the cases treated die within five years. Penicillin seems effectively to arrest the disease in a much larger proportion of cases.

Dattner (1948), in New York, has recently summarized his observations on 151 patients treated with penicillin alone; among these were 33 cases of general paralysis and 19 cases of tabo-paresis, and in all but two of these the results of treatment were satisfactory in that the spinal fluid syndrome indicated an arrest of the disease process. In two cases of general paralysis the results were recorded as indefinite because the cerebrospinal fluid showed 4 or 5 cells per c.mm., and therefore further treatment was undertaken or proposed.

Such statistics are much superior to those recorded with malaria. Stokes and his colleagues (1948), trying to assess their results on a clinical basis, believed that the immediate clinical improvement in cases of general paralysis was greater after malarial therapy than after a course of penicillin; but now having followed their cases into the third year they are obviously more impressed with the effects of penicillin therapy. Among their conclusions are the following:—

“Malaria in paresis is superior to penicillin alone in the clinical improvement

seen before it was introduced. As it is with this type of case that Herxheimer reactions are most likely to occur, I may mention again that I have observed no such effects with penicillin treatment.

TABES

Tabes is a slow disease in which most of the symptoms seem to be due to changes of a degenerative nature, and whether or not any actual recovery in the degenerated tissues can be expected from any method of treatment is open to question; probably the most that can be anticipated is that the disease may be arrested. As its evolution is so slow, however, years must elapse before any confident opinion can be formed as to whether it has been arrested or not. In many cases the indications are that the infective process is not very active, and treatment with penicillin or with arsenicals soon renders the cerebrospinal fluid inactive, and in the course of a number of months afterwards it reverts to normal. The patients are better subjectively and their lightning pains are diminished or abolished, but the essential physical signs of tabes, as would be expected, remain unchanged, and from the nature of the disease it must take many years to determine whether it is arrested or not.

OPTIC ATROPHY

Optic atrophy, because of the patient's greater appreciation of his plight, presents problems at least as worrying to the physician as those of general paralysis of the insane. Cases vary enormously in the rate of progress of the atrophy, and consequently the effect of treatment is sometimes hard to judge. With the older methods of treatment it was unusual to secure more than a retardation of the onset of blindness, but in occasional cases some sight was saved. Treatment with malaria produced somewhat better results, and although in this field experience with penicillin is still limited, it seems so far that the results obtained by penicillin treatment are still better than those obtained with malaria. This is probably because of the quickness of its action and the greater promptness of the arrest of the infective, and possibly toxic, process.

The first patient of this kind whom I treated with penicillin was already blind in his right eye before he came under observation, and vision was beginning to fail in his left eye. After treatment the sight of his left eye recovered to a normal state, and now after an interval of three and a half years it still maintains normal vision.

In the second case, the progress of the visual failure seemed to be arrested after a course of penicillin had been given, but in the subsequent eight months there was further deterioration of sight and a second course of penicillin was administered. No further deterioration of his sight was observed in the following two years, at the end of which time the patient died of carcinoma of the bronchus.

Earl Moore (1947) and other American observers have also reported greater success in the treatment of optic atrophy with penicillin than with the older remedies.

of the treatment, and if an effective treatment has once been given no greater or quicker improvement can be obtained by a multiplication of therapies. Of the permanence of the cure the only criterion is the return of the cerebrospinal fluid to normal, and this is obtained as effectively with penicillin alone as with a combined therapy.

Other therapeutic measures.—The same considerations apply to treatment with arsenical preparations and bismuth, and it remains to be seen whether or not there is now any place for them in the treatment of nervous syphilis. For mercury and iodide the position is possibly a little different, since these substances seem to have a special value in bringing about the absorption of gummatous formations, and may therefore help the dispersal of the innumerable granulomatous elements which are present on the meninges and in the blood vessels and cerebral tissue. For this reason I think mercury and iodide should be given; a mixture of the old-fashioned type, e.g.:—

Potassium iodide	10 to 20 grains (0.65 to 1.3 g.)
Solution of mercuric chloride.....	30 to 60 minims (1.8 to 3.6 ml.)
Arsenical solution.....	1 to 2 minims (0.06 to 0.12 ml.)
Chloroform water.....	to $\frac{1}{2}$ an ounce (14.2 ml.)

May be employed alone, taken three times daily after meals, or may be used in association with the inunction of mercury ointment, 4 g. daily, for four to six weeks.

MENINGOVASCULAR SYPHILIS

It is a matter of historical knowledge that meningo-syphilis is less resistant to treatment than general paralysis, and penicillin has in consequence been more readily accepted as an adequate remedy for this type of neurosyphilis. Here again, the effects of penicillin treatment, of the same dosage and intensity as given on page 364, have been to abolish the evidence of active infection, and in consequence to allow clinical improvement to occur. There is a widespread idea that the outlook for recovery in cases of meningo-vascular syphilis can be regarded optimistically, but whereas this is true for the relatively minor manifestations, it must be recognized that if the symptoms indicate any severe damage to the central nervous tissues, recovery is bound to be imperfect. This applies particularly to most cases of vascular lesions and to cases of transverse myelitis, but it also applies, in a lesser degree, to the cases which present signs of a rise of intracranial pressure resulting from meningitis and consequent hydrocephalus. Arterial disease and gummatous formations are responsible for most of the meningo-vascular manifestations, and, as already indicated, I consider that in all such cases mercury and iodide have a place in the treatment, and in all severe cases of meningovascular syphilis I am accustomed to employ mercurial inunction. Except in so far as penicillin produces a more prompt relief of symptoms than the older methods of treatment, it is, in my experience, difficult to say that the results obtained are any better than those

seen before it was introduced. As it is with this type of case that Herxheimer reactions are most likely to occur, I may mention again that I have observed no such effects with penicillin treatment.

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CONCLUSION

Penicillin dominates the modern treatment of neurosyphilis: what place is left for the older remedies, it is still too early to say. Penicillin is so prompt in its action in overcoming infection that the lag of clinical recovery has become more apparent than it was with slower methods of treatment, and so it is more necessary to emphasize that in many instances, and particularly in general paralysis, clinical recovery requires time. Time is also required for the abnormal reactions in the cerebrospinal fluid to subside. If a course of penicillin amounting to not less than five million units has been given, the patient should subsequently be kept under clinical observation and, assuming that the clinical condition is satisfactory, an interval of at least six months may be allowed before the cerebrospinal fluid is again examined. It may very well be found then that the Wassermann reaction is negative and the amount of protein normal, or almost so, but the one feature which, at that stage, determines whether future treatment is required or not, is the cell count. If the number of cells is not more than three per c.mm. no further treatment is called for, but in the event of four or five cells per c.mm. being present, the position must be regarded as doubtful and another examination of the fluid should be made after a further interval. If the number of cells is greater than five, a further course of penicillin should be proceeded with.

Many questions remain to be solved. Only the lapse of time will determine convincingly whether or not penicillin is to supersede malaria for all cases of paresis, and whether tryparsamide and other arsenical drugs are still to be used in neurosyphilis. The dosage of penicillin and the length of treatment have to be standardized and the method of administration has to be simplified; doubtless before long the treatment will be made much easier both for patient and doctor.

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THE TREATMENT OF CONGENITAL SYPHILIS

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THE title of this article implies a reproach to the medical profession, to the community, and to society in general, because congenital syphilis is preventable and could be prevented to a greater extent than it is at present. The amount of congenital syphilis is a measure of the social well-being of a community. The danger with which syphilis threatens the infant is serious, and the handicap which it imposes on the older child is severe. All the circumstances attending its occurrence are such as to destroy happiness, evoke misery and menace the stability of the family and the home. In penicillin the means of prevention is at hand, and is so highly effective that transmission to the next generation could virtually be eliminated. The only satisfactory way to deal with congenital syphilis is to prevent it by ensuring the earliest possible detection of syphilis in the expectant mother and, when detected, attacking it with penicillin and so protecting or curing the disease in the foetus.

ANTENATAL TREATMENT

The ideal to be aimed at is that every pregnant woman should have her blood tested for syphilis, early in the pregnancy at her first examination, and that the tests should be repeated at mid-term and in the last weeks. The object of the early and repeated blood tests is that treatment, if required, is started as early as possible and, if necessary, continued throughout the pregnancy. Recent publications assessing reasonably large groups of cases indicate this astonishing fact, namely, that penicillin will protect or cure the foetus even if treatment is only begun so late in the pregnancy as the last eight weeks, or even later. Such a delay in beginning treatment, if the therapy were to consist only of the traditional arsenicals and bismuth, would involve a significant risk of failure to prevent transmission to the foetus. In those cases which have escaped recognition until the pregnancy is far advanced, penicillin is much more effective than the conventional metal chemotherapy. But, even so, the ideal is an early start in treatment. After one course of penicillin the Wassermann reaction of the blood may remain positive with a high titre of intensity not tending to decline. Re-treatment then becomes necessary, and the addition of bismuth to prolong the therapeutic effect may seem desirable. In such circumstances early recognition of the disease in the mother and the early inception of treatment leave time for a second course of penicillin and for adjuvant medication with bismuth to be completed before term.

Incomparably the best treatment for congenital syphilis is its prophylaxis through adequate antenatal serological testing and through the application of early and appropriate treatment during the pregnancy. The primary consideration, then, is appropriate treatment for the expectant mother, and this in turn will depend upon the stage of advancement of the disease and on the presence or absence of complications.

Syphilis in pregnancy may be in the primary, secondary or tertiary stage. If in the tertiary stage it may be relatively benign, or it may have involved and produced more or less serious disorders of the cardiovascular and/or central nervous systems. Transmission to offspring is most likely in the first five years of the disease, and becomes progressively less probable with the passing of time. The secondary stage with its characteristic manifestations may last for from six months to a year, or be spread out with the recurrence of typical signs over two years or even longer. Spirochætes are most easily recoverable from the moist papules of the skin or from the mucous membrane lesions of the first year. Thereafter the lesions contain so few spirochætes that their demonstration in serum extracted from the lesions becomes much more difficult, or impossible, and is definitely impracticable as a diagnostic procedure for the late secondary rupial patches or for the tertiary gummatous ulcerations. Nevertheless, even in these latter stages, there may be recurrent episodes of spirochætæmia with consequent risk of spread to the fœtus by the perivascular lymphatics of the umbilical vein.

PENICILLIN THERAPY

Penicillin is the treatment of first choice for combating syphilis in the pregnant woman, and its unassailable pre-eminence derives from two weighty reasons. First, as contrasted with the arsenic and bismuth derivatives, penicillin is non-toxic. Secondly, it is more effective in curing or warding off congenital syphilis in the fœtus than arsenicals or bismuthials, either singly or in combination. Now this outstanding success of penicillin in coping adequately with the congenital form of syphilis is thrown into greater relief when considered in relation to its insufficiency in combating the early stages of the acquired form of this disease. Assessing the results of some 40,000 case records of the American cooperative clinical groups, Earle Moore deduced that the failure rate of treatment with penicillin in patients with early syphilis after eighteen to twenty-four months of observation was in the general range of 25 to 35 per cent. This portentous relapse rate in early syphilis in general contrasts most strikingly with the extremely low rate of failure of penicillin to arrest congenital syphilis, which is estimated at only 1 or 2 per cent. (Moore, 1948). Although it is claimed that these extremely favourable results can apparently be achieved by so low a total dosage of penicillin as 2.4 mega units, the dosage advised and actually employed in the Edinburgh clinic is graduated according to the stage of

the disease and is the same as in early syphilis in general, namely, for primary syphilis, if sero-negative, 5 mega units, if sero-positive, 6 mega units; for early secondary syphilis, 10 mega units, and for late secondary, 12 mega units. These totals may seem unnecessarily and extravagantly large, but the failure rate increases significantly when the dosage is reduced, especially below 1.2 mega units and, although it has been hinted at (Moore, 1948), it has not been proved that there is any disadvantage in using such a high dosage of what is essentially a non-toxic agent. Moreover, whether attained by a three-hourly individual dose of 100,000 units or a daily prolonged action dose of 600,000 units, dosage at these levels ensures an adequate time-spread of not less than six days.

Reactions.—In about 40 per cent. of cases of early syphilis the inception of treatment is accompanied by characteristic systemic and local disturbances. This phenomenon is known as the *Jarisch-Herxheimer reaction*. In this country it is peculiar to syphilis and is therefore of some importance in diagnosis. A Herxheimer reaction is usually expressed as a febrile rise of temperature and an aggravation of the chancre and/or the secondary skin rashes. When penicillin is used in treatment, the symptoms come on in four to eight hours after the first injection and usually pass off within twenty-four hours. So far as the management of the average case of early syphilis is concerned this disturbance is not sufficiently severe to call for any modification of the treatment. The circumstance of the patient under treatment being pregnant need not be regarded as materially accentuating the importance of a Herxheimer reaction. If the foetus is already moribund when treatment is started a severe reaction in the mother might conceivably accelerate the inevitable death. There is no reliable evidence that penicillin tends to produce abortion, either through Herxheimer reactions or through exercising a toxic effect (Goodwin and Moore, 1946).

In regard to *methods of administration* of the penicillin the choice lies between three-hourly intramuscular injections, each of 100,000 units of the sodium salt in aqueous solution, preferably the pure white crystalline penicillin-G rather than the yellow amorphous product, and once-daily intramuscular injections each of 600,000 units of either procaine penicillin suspended in 2 ml. of oil or of calcium penicillin suspended in 2 ml. of oil containing 4.8 per cent. of beeswax (P.O.B.). The former method of three-hourly round-the-clock injections necessitates taking the patient into hospital or a nursing home, whereas the latter techniques of once-daily injections allow of ambulant treatment and may be employed if the patient is unwilling to come into hospital. There is reason to believe (Ingraham *et al.*, 1947) that the three-hourly technique is preferable if treatment is only started very late in the pregnancy, although experience with early syphilis in general induces the expectation that the prolonged action methods should be at least as good as the three-hourly method.

Serological tests.—Provided the treatment has been started early in the

pregnancy, after its completion the serological tests, Wassermann and Kahn, should be taken fortnightly and if the degree of positivity of these tests remains high and does not decline within an observation period of three months, then re-treatment should be undertaken. For the accurate assessment and estimation of the position it is essential to use a quantitative Wassermann or Kahn test in which the degree of positivity is expressed in figures corresponding in the Wassermann to the number of doses of complement fixed.

COMBINED THERAPY

Mention has been made of the possibility of employing metal chemotherapy for the prolongation of therapeutic activity beyond the comparatively limited duration of the penicillin course. There are obvious and possibly grave disadvantages in this procedure: arsenic is a highly toxic drug and pregnant women are especially liable to its most dangerous toxic effects, for example, encephalopathy (Speiser *et al.*, 1945) and hæmorrhagic purpura. In view of the outstanding success of penicillin in preventing congenital syphilis in the child there seems to be considerable justification for using it alone in pregnancy (Goodwin and Moore, 1946) and deferring the more dangerous metal chemotherapy until after the confinement. Nevertheless, it is also true, and not inconsistent with what has been said about the liability of pregnant women to the toxic effects of metal chemotherapy, that for the most part expectant mothers stand up to the ordinary organic arsenicals, neoarsphenamine and oxophenarsine, astonishingly well, and that in the past the arsenicals and bismuth in combination have achieved a substantial measure of success in arresting prenatal transmission. Moreover, the arsenicals and bismuth have stood the test of time, and if used in sufficient dosage and in sufficiently prolonged time-spread can achieve a very much higher cure rate in non-pregnant cases than can penicillin, or, to put it in another way, are attended, under ideal conditions of administration, by a failure rate of about one-third to one-quarter that of penicillin (Moore, 1948). If then the influence of tradition should sway the decision in favour of arsenic, the safest *arsenicals* for use in addition to penicillin are the pentavalent acetarsol (acetylarsan), given by intramuscular injection in a dose of 2 to 3 ml. twice-weekly, or the trivalent oxophenarsine (mapharside or neohalarsine), given by intravenous injection in a dose of 40 mg. twice weekly. These arsenical drugs should not be continued for longer than eight to ten weeks without allowing a rest interval of three to four weeks. *Bismuth* given by intramuscular route may be administered as the sole adjuvant of the penicillin or in combination with the arsenical. Suitable preparations of bismuth are the B.P. injection (finely divided bismuth metal suspended in a solution of glucose, carrying a dose of 0.2 g. in 1 ml.), in a dose of 1 ml. per week, or a 10 per cent. suspension of bismuth salicylate in oil (e.g. bisantol), the weekly dose being 2 to 3 ml. The bismuth injections are given in courses of eight to ten weeks separated by intervals of three to four weeks.

The mother's treatment and observation are continued in the usual way after her confinement and, if she has responded well and has passed satisfactory tests of cure, she need not be re-treated during a subsequent pregnancy (Speiser *et al.*, 1947).

THE MARASMIC INFANT

If the omission or lack of the indispensable serological tests during the pregnancy should allow the syphilis to remain undetected, the effect on the child will vary according to the duration and intensity of the disease. Virulent syphilis acquired by the mother at the time of, or within the year preceding, conception may kill the foetus *in utero*, the death of the foetus usually occurring later than the fourth month. Recent virulent disease tends to produce a stillborn premature foetus rather than early miscarriage. Syphilis seldom kills the foetus before the fourth month, so that treatment of the mother by penicillin started before the fourth month is highly likely to save the life of the child. But if the beginning of treatment should be delayed until the sixth or seventh month the foetus may already be moribund and the inception of treatment too late to save it. Thus a foetus may be born dead after treatment is begun, and there is little evidence to indicate that a severe Herxheimer reaction in the mother is liable to result in precipitating the impending and possibly inevitable foetal death.

Even when the effect of recent syphilis on the foetus is severe, it may escape death *in utero*, especially if of the female sex, and be born alive but prematurely and enfeebled by syphilitic toxæmia. These premature marasmic babies may show what has been traditionally accepted as the classical picture of a syphilitic infant: the old woman or old man face, the withered-looking sallow café-au-lait skin, the shrunken limbs and thin chest contrasting with the prominent abdomen pushed out by the enlarged liver and spleen, the hoarse cry and the aura of impending death. But a picture like this is exceptional and nowadays is seldom seen, possibly because the disease has lost some of its former virulence. Obviously the life of such a severely affected marasmic infant is precarious and even penicillin may fail to avert the death which is looming so near. Obviously, too, this scarcely viable body is not adapted to withstand therapeutic shock of Herxheimer type induced by any potent remedy.

Treatment.—Penicillin should be tried, but cautiously and in a dosage related to the body weight. For these feeble infants the total dosage as determined by the body weight should be in the range of around 80,000 units per kg. (2 lb. 3 oz.) divided into 100 injections given at three-hourly intervals for a period of 12½ days. The total dose for an underweight infant of 2½ kg. (5 lb. 10 oz.) would be 200,000 units. Greater safety may be ensured by reducing the initial individual doses to 1000 units for the first 20 injections, and then 2000 units may be given three-hourly for the next 90 injections, making a total of 110 injections. If the weakly baby survives, the treatment may be continued with twice-weekly intramuscular injections of

the B.P. injection of *bismuth* diluted to 1 part in 9 parts of glucose solution, the diluted product carrying 0.02 g. in 1 ml. The initial bi-weekly dose of the diluted bismuth may be as low as $\frac{1}{3}$ ml. (representing 0.0066 g. bismuth) and the dose should be increased gradually to $\frac{1}{2}$ ml. When the dose is increased to 1 ml. the interval between the injections may be lengthened to one week. The bismuth injections may be continued for from four to six or eight weeks. The duration of treatment will be determined by the titre of the quantitative Wassermann, and by whether or not the tests of the cerebrospinal fluid have shown involvement of the central nervous system. A case complicated by central nervous system involvement, or one in which the titre of the Wassermann remains high and does not decline, will require multiple courses of penicillin. When viability has been definitely established, an arsenical as well as the bismuth may be administered in the intervals between the multiple penicillin courses. When dealing with these grossly infected babies any arsenical must be used with caution. The least toxic one is the pentavalent *acetarsol*. There is a preparation for infants of the proprietary drug, acetylarsan, the ampoules of which contain 0.04 g. in solution in 2 ml. In order to test tolerance the initial intramuscular dose given twice weekly may be as low as $\frac{1}{3}$ ml. (=0.0066 g.). This dose is gradually increased to $\frac{1}{2}$ ml. and 1 ml. When the dose reaches 2 ml. the interval separating the injections may be lengthened to one week. The arsenical may be continued for from five to ten weeks, and on completion of the course a rest interval of three to four weeks should be allowed.

The important question of whether or not adjuvant arsenic and bismuth should be used in conjunction with multiple courses of penicillin is one which can be settled only by the test of prolonged observation. There is evidence to prove that penicillin used alone can produce better results in combating neonatal congenital syphilis than it can achieve in eradicating early acquired syphilis in adults (Moore, 1948). But years will elapse before it can be known whether these neonatally treated cases will or will not show tardive signs of the disease later in life. The old traditional treatment with arsenic and bismuth has proved itself over the years, and it may well be argued that these innocent victims should have a conventional metal chemotherapy "cure" as well as a penicillin "cure", the word "cure" being used with all due reserve. After all, it is very remarkable and extraordinary that penicillin should fail less often in curing these babies whose viscera—liver, spleen, heart and lungs—are literally teeming with spirochaetes, especially when one considers its estimated 25 to 35 per cent. failure rate in adult acquired syphilis.

Fortunately the very severely infected premature cases do not occur sufficiently often to constitute a serious problem. More usually the congenital syphilitic baby is born at full term apparently healthy and begins to show such signs as "snuffles" or a maculopapular rash on the face and buttocks only after three to five weeks of extra-uterine life. Such babies are commonly quite well nourished and their treatment can be much less

tentative. For the most part they do well on penicillin and the beginning three-hourly dose need not be smaller than 5000 units. After forty-eight hours any Herxheimer intensification of signs will have passed off and the individual dose may be increased to 10,000 units for 10 injections until a standard three-hourly dose of 25,000 units is reached. The course should be continued until 2, $2\frac{1}{2}$ or 3 mega units have been given. Cases treated with penicillin alone must be kept under constant and regular observation with fortnightly quantitative Wassermann tests of the blood, in order that any failure of the Wassermann to decline steadily in titre to a maintained negativity may be met by re-treatment. Rather than wait for serological failure or relapse to declare itself, many clinicians will prefer not to depend upon a single course of penicillin, but to give multiple courses and also use metal chemotherapy, which is usually well tolerated by these stronger infants.

When treatment is not begun until the child is several months old, and when there is no serious malnutrition, *arsphenamine diglucoside* (stabilarsan) may be used to supplement penicillin. This trivalent arsenical may be given intramuscularly, twice weekly in a dose of 5 mg. per kg. of body weight, or once weekly in a dose of 10 mg. per kg. body weight. The weekly dose for a child of 11 lb. would be 0.05 g. This arsenical is easily given because it is already in solution in the ampoule, and a suitable course might consist of six weeks of twice-weekly or eight weeks of once-weekly injections.

With regard to *the duration of treatment* for these infants, in the pre-penicillin days it was quite usual to give continuous treatment for six months, using an arsenical and bismuth alternately rather than allowing rest intervals. After the first six months the arsenical, say *arsphenamine diglucoside* (stabilarsan), and diluted bismuth in doses appropriate to body weight, could be given concurrently, in courses separated by rest intervals of three to four weeks. The maintenance of treatment for a year was not considered an excessive prolongation even for cases uncomplicated by involvement of the central nervous system. Thereafter followed clinical and serological observation at three-monthly intervals for two years. Positive findings in the tests of the cerebrospinal fluid constituted an important indication for additional courses of treatment and for extended observation.

PENICILLIN ALONE OR COMBINED THERAPY?

To what extent is it allowable to accept the undoubted immediate success of penicillin in early congenital syphilis as a reason for cutting down the duration of treatment, and what amount of curtailment is justifiable? On these questions opinions will vary, and the answers given will differ from extreme divergence to middle-course compromise. Some clinicians will rely on penicillin alone in one course with re-treatment in the event of serological relapse. At the other end of the scale will be some who will use penicillin only as an addition to, and not in any degree as a substitute for, the conventional arsenical and bismuth chemotherapy. As a compromise,

some will seek to reinforce penicillin with subcurative amounts of arsenic and/or bismuth, in spite of the fact that statistics for early acquired syphilis in the adult do not support the theory of a synergistic action of these three agents (Moore, 1948).

Confidence in the ability of penicillin alone to deal adequately with congenital syphilis is not increased by an investigation of its action when it is used in tardive congenital syphilis in the hope of its controlling such characteristic and potentially disastrous manifestations as interstitial keratitis and eighth-nerve deafness. Granted that interstitial keratitis is a peculiarly intractable process of allergic type and that nerve deafness may progress in fulminating fashion to its terminal catastrophe of complete destruction of hearing; even when all allowances are made, the hope that penicillin will work wonders is doomed to disappointment, and the deduction is unavoidable that if penicillin can fail in these older girls and boys it may fail in infants also. The discovery and recognition by school medical and dental officers of such signs as Hutchinsonian incisor teeth, or Clutton's hydrarthrosis of the knee joints, leading to treatment of the seven- or eight-year olds, would forestall and possibly prevent complications, such as interstitial keratitis, nerve deafness, juvenile paresis and juvenile tabes, which tend to arise later on towards puberty.

In the treatment of *congenital syphilitic children of school age*, the best results accrue from a combination of penicillin with arsenic and bismuth. Girls and boys of eight to fifteen years, and older adolescents tolerate metal chemotherapy exceedingly well. A twelve-year-old of average weight may be given neosarsphenamine intravenously in doses of 0.15 g. twice weekly, or 0.3 g. once weekly. Intramuscular bismuth may be administered concurrently in doses of 0.1 g. to 0.15 g. weekly. The dosage of penicillin, graduated according to body weight, approaches nearly to the adult range, a suitable standard three-hourly dose being 50,000 units, which is continued up to a total of 5 to 10 mega units. For resistant cases of interstitial keratitis a useful adjuvant is *fever therapy*, induced preferably by inductopyrexia.

Penicillin does not solve all the problems presented by these tardive cases, and its relative non-success forces a return to the assertion with which this article was begun, namely, that the only satisfactory solution to all the problems is the elimination of congenital syphilis through recognition and treatment of the disease in the expectant mother.

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MODERN VIEWS ON DIAGNOSTIC TESTS IN SYPHILIS

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WITH the advent of penicillin it was hoped that the incidence of syphilis would soon be reduced to negligible proportions, and great demands were soon made upon the laboratory to provide more accurate and precise information in reports on the examination of sera. As a result of this, much research work was done and the sensitivity of the serological tests employed was greatly improved.

In this country, the most commonly used serological tests are the Wassermann reaction, and one or other of the precipitation tests, such as the Kahn, Laughlen, Price's precipitation reaction, the Sachs Georgi and the Meinicke tests. Tests are employed now much more often than they were, not only during the treatment of the disease but also in routine testing of pregnant women. Before the war, the latter section of the community hardly troubled the laboratory, but as the war progressed, increasing numbers of specimens from this source were sent for testing and the value of this procedure was soon proved.

TESTS EMPLOYED

As has already been stated, the serum tests used in the diagnosis of syphilis are divided into two classes: a complement fixation test, such as the Wassermann reaction, and the various precipitation tests. Of the two it may be said that the sensitivity of the Wassermann reaction has been increased in recent years, and the test should be regarded as the most reliable of all the tests employed.

It is of interest to note that a specially purified antigen called "cardiolipin" for use in the *Wassermann reaction* has recently been evolved in America. This is claimed to be a chemically pure substance, and is said to give much better results when used in the test than the ordinary ox heart extract antigen as used in this country. I have tested 1,982 sera in parallel, using both antigens, when 96 per cent. of the results obtained agreed. Of the disagreements, 4 per cent. (80 sera), the results of the Wassermann reaction when cardiolipin antigen was used seemed to be somewhat more sensitive, with no loss of specificity. However, many more sera will have to be tested before a final decision can be made.

Precipitation tests, on the other hand, are easier to perform, take less time to do, and a preliminary report on a serum can be issued often within a few hours. Nevertheless, it is generally agreed that the Wassermann

reaction should be the standard test and precipitation tests should be used in a confirmatory capacity.

Cerebrospinal fluids are examined by the Wassermann and the Price's precipitation reaction. Of these two tests the Wassermann may be a little more sensitive, but during an investigation of 284 cerebrospinal fluid tests in parallel with the Wassermann and the Price's precipitation reactions there were no disagreements, both tests recording 13 positive and 271 negative results respectively. It is of interest to note that as a rule the cerebrospinal fluid of patients with general paralysis of the insane give a positive result with higher dilutions of the fluid than do the cerebrospinal fluids of patients with tabes dorsalis when tested by Price's precipitation reaction. On the other hand, the examination of cerebrospinal fluids by the Kahn test is laborious and the results obtained have not been very encouraging.

THE USES OF SERUM TESTS

Serum tests are usually employed in the following circumstances:—

(1) Routine tests as applied to pregnant women and blood donors.

(2) In the diagnosis of suspected disease after a definite exposure to infection with a person known to be suffering from syphilis, or in the case of a patient with gonorrhœa who may at the same time have contracted syphilis.

(3) As a test of cure after adequate treatment for syphilis.

Antenatal serum testing.—There is little doubt that even to-day this investigation is too infrequently undertaken. The attitude so often adopted is that this is quite unnecessary, except in certain classes of the community. Syphilis is no respecter of persons, and no strata of society are immune. Moreover, now that children threatened with congenital syphilis can be guaranteed immunity from the disease in almost 98 per cent. of cases if adequate steps are taken, the neglect of antenatal blood testing seems indefensible. When dealing with the patients themselves blood is usually taken for Rhesus grouping and no mention of a Wasserman reaction need be made, for the same specimen of blood may be used for both investigations. Thus, no patient need suffer any distress unless, unhappily, the serum report for syphilis proves to be positive. It should be mentioned that in the latter event a second examination should be made in order to check the first before the patient is informed. This ensures that, so far as may be, any possible technical error is eliminated.

Blood donors.—Little need be said about blood donors since it is universally admitted that all patients receiving blood should be protected from accidental infection by the use of blood containing *S. pallidum*. When the source of blood for transfusion is from a blood bank there is no danger, because all samples of blood which are sent out have already been tested. Where the danger may occur is on the rare occasions when emergency transfusions are made "on the spot".

Diagnosis in suspected disease: definite exposure.—Patients who present

themselves to the doctor after definite exposure should, of course, always be tested even when *S. pallidum* has been demonstrated in a lesion. The time after exposure when a positive result may be anticipated in the case of definite infection is very variable, but on average may be said to be within three to five weeks. It must be remembered, however, that this time may be considerably lengthened, even up to a period of twelve weeks. Thus it is advisable to test the blood again even in the absence of any clinical signs. It must be borne in mind that patients suffering from gonorrhœa may also be incubating syphilis and when treated with penicillin may not develop any clinical signs of syphilis for some time. Moreover, their serum reactions may be suppressed by the drug for many months. It is therefore advisable to test the blood of all patients treated for gonorrhœa with penicillin, not only at the onset of the disease, but monthly for three months, and finally six months after the cessation of treatment.

Tests for cure.—Serum tests are, of course, always employed as a test for cure and are usually performed at three-monthly intervals during the first year of observation, at six-monthly intervals during the second year of observation, and at the end of the third year a final test is made. In addition, no patient should be discharged as cured unless the cerebrospinal fluid has been examined and found to be normal.

METHOD OF RECORDING RESULTS OF TESTS

Before the war, efforts were made to induce serologists to report their results in such terms as "positive", "doubtful" or "negative". Unfortunately, there had grown up so many techniques and so many ways of reporting serum tests that except to those familiar with the various methods of performing these reactions the report was often quite incomprehensible, not only to clinicians but even to pathologists. With the development of new techniques matters became worse, but after the war, efforts were made to cope with the situation. Nowadays an attempt is being made to persuade pathologists to report tests in terms of serum dilutions. Thus positive results could be recorded as being positive with definite serum dilutions, for example, "Positive, serum diluted 1 in 40", which indicates that this is the highest serum dilution which records a positive result, and this gives some idea of the reaction of the body against the infection. From this may grow up the technique of recording the positive serum results of a patient under treatment in the form of a graph, thus attempting to show the serological progress of the disease pictorially. This latter method of recording results is not in general use, but has much to recommend it. Unfortunately, although the need for standard methods of recording results is generally recognized, this ideal has not yet been achieved. No doubt in the near future the problem will be solved, and steps towards this end are being taken by the World Health Organization. In the meantime it is suggested that clinicians should demand a simple report stating that the specimen of serum examined is "positive", "doubtful" or "negative",

depending upon which term is applicable. Any further information which the serologist cares to give can then be added.

Thus, a suggested formal report on a serum giving positive reactions would be given as follows:—

Routine Wassermann reaction	Positive
Quantitative Wassermann reaction	Positive serum diluted 1 in 10
Price's precipitation reaction	Positive serum diluted 1 in 2
Routine Kahn reaction	Positive

Such a report would leave no doubt in the clinician's mind.

In the case of borderline serum reactions the report might read:—

Routine Wassermann reaction	Positive
Quantitative Wassermann reaction	Positive serum diluted 1 in 5
Price's precipitation reaction	Negative
Routine Kahn reaction	Doubtful positive

The interpretation of such a report as the above would largely depend upon the history of the patient and the clinical signs. These results may occur in the early phases of the disease, in a case of suspected congenital syphilis, or at the end of treatment, and it will be seen that in the absence of a clinical history the pathologist would be quite unable to give an intelligent opinion. The probability is that the pathologist would require another specimen in order to check on borderline reactions such as these before sending out a report.

On the other hand, a completely negative report would be reported as follows:—

Routine Wassermann reaction	Negative
Price's precipitation reaction	Negative
Routine Kahn reaction	Negative

This would not of necessity disprove the presence of the disease. For instance, the patient may be incubating the disease and the serum may have been tested before the production of "antibodies" has proceeded far enough to be demonstrable. It should be remembered that in any test there is a threshold of recognition, and until this is reached the serum of a patient suffering from syphilis will not record a positive result. In like manner, at the other end of the scale, in a treated case the amount of "antibodies" present in the serum may be just under the threshold of recognition but the disease has not been eradicated, and in such instances a serum relapse followed by a clinical relapse may occur if the treatment has been insufficient. This sequence of events is shown in the following graph (fig. 1).

The graph shows that after what had been thought to be adequate treatment the serum test remained negative for four months. A serological relapse then occurred, followed six weeks later by a clinical relapse. Had this patient been treated when the serological relapse had shown itself, the clinical relapse might have been prevented. Thus in figure 2 it will be seen that after a course of treatment a serological relapse occurred which, on further treatment, resulted in the decline of the strength of the positive

serum test only to be followed by a second serum relapse. Further treatment caused the serum reaction to return to negative and remain there. Clinically the patient showed no signs or symptoms of the disease after the first course of treatment.

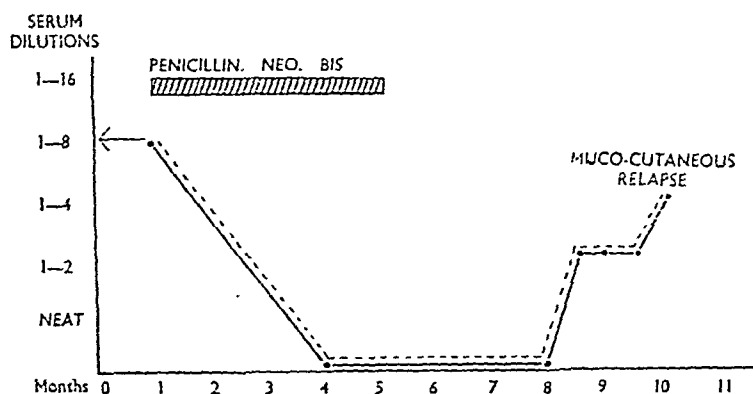


FIG. 1.—Sero-positive primary syphilis. Price's precipitation reaction — : W. R. - - - -

It is hoped that these two graphs will show how useful it is in treated cases to have a pictorial record of the positive results obtained with the serum of patients during a course of treatment. At the same time it must be realized that if a patient is treated early enough in the course of the disease the serum reactions may never record positive results, and in consequence the production of such graphs is impossible.

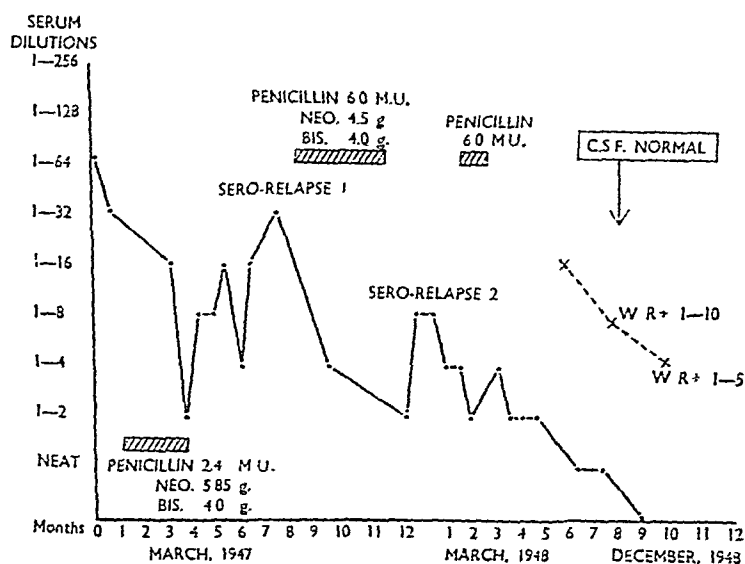


FIG. 2.—Late secondary syphilis.

FALSE POSITIVES

No consideration of modern views on diagnostic tests in syphilis would be complete unless the question of biological false positives was mentioned. A definition of the phenomenon is hard to come by and the number of conditions said to be related to such serum reactions is legion. Among the most common of these in this country are said to be infectious mononucleosis, atypical (virus) pneumonia, scarlet fever, measles and pregnancy. Whilst exact definition is difficult, the one usually accepted is that biological false positive reactions are suspected when repeatedly positive blood tests are given by the serum of a patient who fails to yield any evidence of syphilis. Moreover, on serial quantitative testing the blood test remains positive for a relatively short time but gradually its strength fades until it becomes negative *in the absence of any specific treatment*. There are, however, a few biological false positives which remain positive for such a long time that it is virtually impossible to exclude the possibility of latent syphilis. There is no known way of discriminating between such biological false positive blood reactions and the positive reaction given by serum from a case of latent syphilis, and thus it is in these cases that the laboratory cannot give much help to the clinician. Fortunately, this phenomenon is uncommon, and in a recent examination of 8,276 sera only 7 (0.085 per cent.) were discovered. Even considering the sera sent to the Venereal Disease Reference Laboratory, which all consist of specimens giving anomalous results in other laboratories and are sent for comparative testing, out of 1,036 sera so sent only 12 (1.1 per cent.) could be classed as biological false positives. In other countries, particularly those where tropical diseases are prevalent, the occurrence of these reactions is much more frequent. It would appear that in Great Britain this problem is not so acute as it is elsewhere and the number of times that the phenomenon is likely to be met with by practitioners is extremely few. Nevertheless, the social implications which might arise as the result of such an unfortunate serum result are so grave that the practitioner, if in doubt, should seek the advice of an expert venereologist.

CONCLUSION

From what has been said in the foregoing it can therefore be seen that in the interpretation of serum tests for syphilis it is essential that the clinician should have an idea of the value of the capabilities of the tests employed and how they are to be related to the clinical history. If he is in any doubt he should consult the pathologist.

In conclusion, an appeal is made to practitioners to send a brief account of the history and clinical condition of the patient with all specimens of blood sent for examination. The shorter this statement is, the better, provided it contains the relevant facts, such as the diagnosis, treatment (if any), present state of the patient, and the results of any previous serological tests. Without this information it is quite impossible for the pathologist to give an intelligent interpretation of his results.

THE TREATMENT OF GONORRHOEA

By A. O. F. ROSS, M.D., D.P.H.

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THE problem of the treatment of gonorrhœa was much reduced by the introduction of the sulphonamide drugs, and it is regrettable that certain strains of gonococci proved resistant from the beginning and that others, by reason of insufficient dosage, developed resistance to all members of the sulphonamide series. Apparently it was not the gonococcus alone which was capable of developing this resistance but many, if not all, of the organisms which cause non-specific urethritis, and which are oft-times associated with the gonococcus in its attack upon the urethra and in metastasis to various structures in the body, such as joints or tendon sheaths. This is well demonstrated by observations made in the same clinic on the effect of sulphonamides in the treatment of gonorrhœa. The original report (Prebble, 1940) claimed that the urethral tract was rendered free from pus in 92 per cent. of cases treated with sulphonamides (sulphapyridine). Five years later the second report (Ross, 1945) could only claim that in 37 per cent. of cases was this result achieved, although more potent sulphonamides (sulphathiazole and sulphadiazine) were employed.

The development of the antibiotic substances, in particular penicillin and streptomycin, have further simplified the problem, but the three principles enunciated in the last symposium on the treatment of venereal diseases in *The Practitioner* (May, 1945) are as strongly entrenched as ever:—

- (1) Accuracy of bacteriological diagnosis and investigation of the anatomical areas involved.
- (2) Adequate dosage of the chosen drug over an adequate time period.
- (3) Careful surveillance after cessation of symptoms or apparent cure, to exclude the possibility of residual infection leading to early or late relapse (McLachlan, 1945).

GONORRHOEA IN WOMEN

In women there is often absence of symptoms and signs, and this is borne out by the fact that a women's clinic is supplied with more cases by the efforts of the medical officer of the male clinic than from any other single source. This results from the procedure known as "contact tracing", and consists in prevailing upon the male patient to persuade his female contact or contacts to attend for examination. The attendance of the female contact (often the wife) is facilitated by the male handing her a "contact slip" which is of postcard size and texture, and upon which is printed the name of the senior medical officer together with the address and hours of the appropriate

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in the floor of the urethra and open at the meatal orifice on either side of the middle line. Occasionally, the fact that they are infected is shown by their scarlet colour—a dot no larger than a pin point—or by a mammillated appearance, or by a turgidity of the floor of the urinary meatus. In such an event they should be destroyed by the electric cautery after examination of the genitals is complete. Smears and cultures should be taken from the meatus after stripping the urethra through the anterior vaginal wall with the index finger. Attention should next be directed to the orifice of the Bartholin ducts which lie under cover of the labia minora in the posterior arc of the vaginal introitus. The orifice may appear as a red spot, the so-called “macule of Sanger”, and this should be regarded with suspicion, as should also warty growth restricted to this area.

The Bartholin gland area on either side is then palpated and the gland contents expressed, provided there is no obvious suppurative peri-adenitis. Smears and cultures of the presenting secretion are again taken. A gloved finger is now inserted into the vagina to discover the position of the cervix and the presence of any adnexal abnormality by bimanual examination through the lateral fornices. The examining fingers are withdrawn and a warmed speculum, preferably of the Cusco type but without antiseptic lubricant, is passed, the light adjusted and the cervix exposed. First take a swab of the secretion found in the vaginal vault and return it to the sterile test tube from which it was drawn and to which rather less than 1 ml. of fresh normal saline has been added. This serves as a specimen for examination for *Trichomona vaginalis*, a common concomitant of purulent vaginal discharge. The external os is cleared of secretion by dry swabbing, a flow of fresh secretion is stimulated and smears and cultures made therefrom. Material may then be obtained from the posterior fornix and sent for culture and microscopical examination. Strictly speaking, an infant size glass vaginal speculum should then be passed through the anal canal and scrapings of the rectal wall taken (Clements and Hughes, 1935), but in practice this will seldom be done. Proctoscopic examination has been advocated for more exact work (Nicol, 1948).

The examination of the genital area has now been completed and all possible specimens obtained from the sites for which the gonococcus has a predilection, namely, the urethra with special emphasis on Skene's tubules, Bartholin's glands and ducts, the cervical canal, uterus and appendages, the posterior fornix vaginae, and the rectum. Skene's tubules, if infected, can now be cauterized and warts touched with 25 per cent. podophyllin resin in liquid paraffin. They should first be dried, then the podophyllin suspension applied and the patient instructed to wash the area clean in eight hours and to apply a dusting powder. No pain is experienced and the results are satisfactory. Examination to exclude metastatic gonorrhoea and syphilis, including the taking of blood for the Wassermann reaction, completes the session until the bacteriological reports are returned. In this connexion it cannot be too strongly emphasized that all slides, tubes, and so on, should be marked with the patient's identity before being used for pathological specimens. Unless this is done, mistakes are bound to occur with perhaps regrettable consequences. If the diagnosis is established, treatment follows.

Treatment.—As indicated, it is well to deal separately and primarily with infected Skene's tubules, and the most satisfactory method is ablation

female clinic. In the top right-hand corner the identification number and diagnosis of the male patient are shown.

Dr. Blank, Southern Hospital.		No. _____
		Diagnosis _____
Mon. } 9.30 a.m.-1 p.m.	Tues. } 9.30 a.m.-1 p.m.	
Fri. } 3-6 p.m.	Wed. } 3-5 p.m.	
Sat. } 9.30 a.m.-12 noon	Thur. }	

Although not applicable to private practice it is a most valuable method in hospital work.

Diagnostic tests.—The usual textbook description of discharge from the genitals, dysuria, and discomfort in the lower abdomen may be produced by many conditions other than gonorrhœa, and therefore a diagnosis can only be established by demonstrating the gonococcus in smears and culture. The most meticulous laboratories demand not only culture but sugar fermentation tests, and the like (Macleod, 1947), but for general everyday purposes gram-negative diplococci of the characteristic morphology and grouping are accepted as gonococci. Within recent years many laboratories have paid great attention to the question of culturing gonococci, and it should always be the aim of the practitioner in charge of the case to obtain swabs for culture as well as direct smears. Failure to obtain culture material substantially reduces the possibility of a positive result. A good specimen of secretion taken on a diphtheria swab and sent to the laboratory within two hours may result in the demonstration of gonococci when smears show neither pus nor gonococci. The specificity of the gonococcus complement fixation test is a vexed question: throughout most of the country, laboratories have failed to master the technique and the test is quite valueless. On the other hand, the Wassermann test is a reliable reaction and should be employed to exclude syphilis in every case, and this may require testing over three or more months.

Examination of the genital area.—In the search for diagnostic material from the genitalia, the genital area must be well exposed and subject to good lighting conditions. The lithotomy position and the illumination of a one-hundred watt lamp directed upon the genitals are therefore necessary. No antiseptics must be employed but swabbing with sterile saline is allowed. Care must be taken not to overlook any eroded areas and, if these are found, capillary tube specimens of their serous exudate must be obtained and sent for dark-ground examination to exclude primary or secondary syphilis. Should an eroded area be found externally, and especially if the inguinal glands are unilaterally enlarged, no penicillin should be given before primary syphilis is excluded by frequent testing. The presence of warts should be noted and treatment for them given before the patient leaves the table. Next, attention should be directed to the ostia of Skene's tubules, which lie

three weeks of life, are secreting mucous membranes and are liable to infection by the gonococcus. Occasionally the cervix is infected and the disease may involve uterus, tubes, and peritoneum.

Diagnosis is bacteriological, by demonstrating the causal organism in culture. Non-specific and nematode infections may produce vulvo-vaginitis.

Treatment.—So far as possible, and more especially in older girls, treatment should not be specifically local but should consist in antiseptic hip baths, for the sake of cleanliness, together with the administration of sulphonamides. A daily dose of sulphathiazole or sulphadiazine, $\frac{1}{2}$ a grain (32 mg.) per pound of body weight, should be continued for one week. The daily dose should be divided into four equal parts, given with an effervescent drink four times daily after food.

Penicillin is not as a rule successful in the treatment of this disease and sulphonamide treatment should first be tried. If relapses occur, then penicillin therapy must be considered. Preliminary treatment with stilbœstrol, 0.5 to 1 mg. thrice daily, until the vaginal epithelium has keratinized—say, three to four weeks—should be given and then 150,000 units of procaine penicillin twice daily on six occasions, injected into the glutei or external quadriceps.

Smears and cultures should be made frequently over a period of three months to ensure freedom from relapse.

In all cases an effort should be made to discover the origin of the trouble, e.g., an infected mother or nursemaid, otherwise re-infection may occur. It is well to take measures by means of special clothing that the child's hands do not become contaminated and ophthalmia develop as a result. The child must be segregated from her fellows in every possible way, to prevent spread of infection.

OPHTHALMIA BLENNORRHAGICA

The clinical recognition of this disease calls for immediate active measures without waiting for bacteriological proof.

If one eye only is affected protection of the sound eye by a Buller's shield is a wise precaution, although the effects of penicillin treatment in this condition are so immediate and complete that infection of the sound eye after treatment has been instituted must be rare.

Local treatment for the first three hours must be given every five minutes with penicillin solution, 2,500 units per ml. Thereafter, treatment should be given every half-hour until the complete absence of moisture, redness and swelling allows less frequent application (Sorsby, 1945).

Oral treatment with sulphathiazole in the dosage prescribed for vulvo-vaginitis is of value and ought to be given.

GONORRHOEA IN THE MALE

Although the advent of penicillin has rendered success in treatment rapid and trouble-free in the majority of cases, it must not be assumed that all

by the electric cautery. In some cases—and it is a method which should be given a trial when a cautery is not to hand—the injection into the area of 100,000 units of penicillin in 2 ml. of sterile distilled water has proved curative.

In the presence of much discharge it is better to control this by appropriate measures before dealing with multiple warts. The presence of trichomonas is responsible for, or coincides with, much discharge even in definite gonorrhœal cases, and the employment of acetarsol vaginal compound in efficient dosage reduces rapidly the amount and the associated discomfort. Four tablets should be used thrice weekly, roughly on alternate nights. They should be moistened by semi-immersion in a little water, while the patient washes her hands and vulva, and then introduced as high as possible into the vagina. This routine should continue for eight weeks whether the menstrual flow is present or not. This is as a rule sufficient to cure the condition, but checks should be maintained for several months.

At the present moment the ideal treatment for genital infection is the injection of *penicillin* in oil wax, or procaine penicillin in arachis oil emulsion, by single shot of 300,000 units. For rectal infection, sulphathiazole or one of its derivatives, such as phthalylsulphathiazole, must be used in addition. One week later smears and cultures from the possible sites of infection are repeated, and if these prove negative the patient is asked to report within two days of the end of her menstrual flow for further testing. Finally, if all remains negative for three months a dose of gonococcal vaccine equal to 200,000,000 gonococci is given endodermally and a thorough investigation is carried out forty-eight hours later. A blood Wassermann test is then done to exclude syphilis, and if the patient is pregnant this is repeated monthly until delivery.

Complications.—Few complications are likely to be encountered which require additional treatment. Suppurative *peri-adenitis of Bartholin's glands* is treated by aspiration of pus and its replacement by 100,000 units of penicillin in aqueous solution. More radical surgical treatment is rarely required.

Arthritis and tenosynovitis, the most common of the metastatic type, may respond to ablation of the Skene's tubules together with high dosage of penicillin (500,000 units daily) over a period of a week or more, or of sulphphonamides; but generally, pyretotherapy and physiotherapy are necessary to restore normality, and hospital treatment is indicated.

Salpingitis requires similar high and sustained dosage of penicillin.

VULVO-VAGINITIS IN CHILDREN

This disease is usually contracted from inanimate objects such as towels, thermometers used in taking rectal temperatures in a children's ward, and the like, and is rarely acquired from the male direct. The areas involved are the urethra, vulva, vagina and rectum. The mucous membrane of the vulva and vagina of the girl under the age of puberty, except for the first

three weeks of life, are secreting mucous membranes and are liable to infection by the gonococcus. Occasionally the cervix is infected and the disease may involve uterus, tubes, and peritoneum.

Diagnosis is bacteriological, by demonstrating the causal organism in culture. Non-specific and nematode infections may produce vulvo-vaginitis.

Treatment.—So far as possible, and more especially in older girls, treatment should not be specifically local but should consist in antiseptic hip baths, for the sake of cleanliness, together with the administration of sulphonamides. A daily dose of sulphathiazole or sulphadiazine, $\frac{1}{2}$ a grain (32 mg.) per pound of body weight, should be continued for one week. The daily dose should be divided into four equal parts, given with an effervescent drink four times daily after food.

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GONORRHOEA IN THE MALE

Although the advent of penicillin has rendered success in treatment rapid and trouble-free in the majority of cases, it must not be assumed that all

urethral discharge is of gonococcal origin and that penicillin is the panacea. Diagnosis of the disease remains the practitioner's first care and he must always take urethral smears before embarking on treatment. No end of trouble has arisen from failure to take this simple precaution and much penicillin has been wasted. From failure to examine the case properly, graver mistakes have arisen, and care to exclude primary syphilis in the sero-negative stage is more imperative than ever because of the potent action of penicillin upon the *Spirochaeta pallida*. Purulent balanoposthitis with pus presenting at the preputial orifice may have a specific origin, and examination of this area with the prepuce retracted must be thorough. The faintest suspicion of early syphilis calls for further investigation, and quite definitely no penicillin must be given until syphilis is excluded. *Syphilis d'emblée*, in association with gonorrhœa and latent syphilis from a previous infection, has always called for a serological test for syphilis at the first attendance of a patient with clinical signs of urethritis, and again four months later (Ross, 1930), but more stress is being laid on this to-day because of the action of penicillin in delaying the initial signs of syphilis. Pyrexia within twelve hours of administration of penicillin or a generalized transient angioneurotic œdema is significant in that these symptoms may be the result of the lethal action of penicillin on spirochaetes disseminating through the body. Such cases should be kept under close observation and serological testing for at least three months.

Treatment.—Intramuscular injections of procaine penicillin in oil suspension in two doses of 150,000 units in one day, six to twelve hours apart, will give a cure rate of over 90 per cent. If all patients would refrain from taking alcoholic beverages for a week the percentage would be nearer 100. Therefore it is well to advise against drinking, and of course sexual excitement, until cure is pronounced. Local complications, such as acute epididymitis, may require four such injections in two days. The para-urethral ducts, one on either side of the meatus, and Tyson's ducts, one on either side of the proximal attachment of the frænum, may be infected and require attention. If the condition is a simple ductitis, cauterization with the electric cautery needle is sufficient, but if abscess formation occurs, aspiration of the pus and its replacement with penicillin solution, in a strength of 50,000 units per ml., are the best treatment.

Pus shreds remaining in the urine one week after the administration of the penicillin call for microscopic examination, and if no gonococci are found recourse is had to instillations of the anterior urethra with 5 ml. of 1/500 silver nitrate solution, which is retained for two minutes by manual closure of the meatus. These instillations are given twice weekly, and fewer than six usually suffice to clear the condition.

Metastatic complications.—Arthritis and tenosynovitis have already been discussed under gonorrhœa in women. *Iritis* is a metastatic complication peculiar to the male. Local treatment consists in hot fomentations to the affected eye, together with atropine drops. Pyretotherapy is of more value than any

other form of treatment and may be combined with sulphonamide treatment, but the prime necessity is to clear the genital tract of any focus of infection by assisting drainage from the prostate and vesicles by daily massage. The ducts ought to be rendered patent by the passage of a large sound once weekly.

Tests of cure.—Preliminary tests of cure can usually be begun about fourteen days after the penicillin treatment. By this time there should have been no visible discharge for ten days and the urine should be clear without any pus shreds. A dose of gonococcal vaccine containing 200,000,000 gonococci should be injected endodermally. Forty-eight hours later the site of injection should be free from erythema of greater diameter than one inch, there should be no urethral discharge, and the urine should be free from pus shreds or suspended pus. A large sound should be passed into the posterior urethra and after its withdrawal prostatic exudate should be obtained by massage per rectum. The exudate should be examined microscopically and should contain not more than an occasional pus cell, and no gonococci should be seen or grown in culture. Observation should be continued for three months and syphilis excluded by a serological test at the end of observation.

STREPTOMYCIN

In the not too distant future it is probable that the treatment of choice for gonorrhœa and other urethritides will be the injection of streptomycin. It is thought that one injection of 0.3 g. is sufficient to cure nearly all cases of gonorrhœa (Moore, 1948) and that the more intractable cases of urethritis, such as Reiter's disease, will respond to 0.25 g. given six-hourly to a total of 10 g. (Harkness and Henderson-Begg, 1948). The substitution of streptomycin for penicillin will remove the fears of those who believe that a considerable number of cases infected simultaneously with syphilis and gonorrhœa fail to show signs of syphilis following penicillin treatment for gonorrhœa. Such cases will be infective for a number of years, and instead of being a blessing penicillin will prove a curse unless serological controls are employed.

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THE VENEREAL DISEASE PROBLEM IN TROPICAL AFRICA

WITH SPECIAL REFERENCE TO BRITISH EAST AFRICA

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ALTHOUGH the incidence of the venereal diseases in large tracts of tropical Africa has for many years been known to be inordinately high, the task of estimating accurately the size and shape of the problem is beset with many difficulties. Chief among these are, first, the primitive state of so many of the inhabitants and, secondly, the facts that syphilis and gonorrhœa are diseases that are essentially prone to chronicity and that both of them are characterized by long symptomless, albeit infective, periods.

THE SOCIAL BACKGROUND

The history of the diseases in these territories is of interest, inasmuch that although gonorrhœa seems to have existed from time immemorial, syphilis was probably brought to the West African Guinea Coast early in the sixteenth century, soon after its importation into Europe from the Americas, and was probably only introduced into East Africa by the Arabs in the middle of the nineteenth century, where it is known to have been a comparatively rare disease until the late eighteen-nineties.

The greatest obstacle to the spread of these infections was undoubtedly the rigid tribal customs and taboos with their severe sanctions against promiscuity, especially in women, and it is a sad paradox that the advent of the traders and missionaries, bringing with them their different facets of European "culture", has been largely responsible for a too rapid de-tribalization, with a consequent emancipation of women and an amelioration of the punishments for breaches of the sexual code. Intelligent missionaries, both catholic and protestant, are under no illusions about this fact and consider that, even under the best of conditions, the substitution of the notion of self-control for tribal control will take generations to accomplish. Many missionaries believe that certain tribal customs could be retained with advantage and that this might tide the African over a most difficult period in his evolution. Meanwhile, the conditions for the spread of venereal disease have become increasingly favourable. Communications are improving daily, resulting in frequent movements of populations; men and, to a lesser extent, women, are leaving their families to work in areas settled by Europeans—this is especially so in Kenya—and prostitution, which is rife in these areas, is not yet regarded as a moral or even as a social

offence. As well as this, there is an unslakable thirst for what the African calls "education"; this, although it is in large part provided by mission schools, seems to be designed chiefly to convert the potential manual worker and food grower into a clerk capable of appreciating a collar and tie existence and of understanding the erotic dialogue of the movies.

This then is the background against which any programme for the control of these diseases should be viewed and it should constantly be remembered that, whatever medical measures are taken against them, these will in the long run be ineffective unless there is at the same time a concerted attack against the social sickness of which they are but symptoms.

Whilst much has been said and a little written to the contrary, it seems that both gonorrhœa and syphilis run much the same course in tropical Africa as they do in more temperate climates, and the apparent frequency of complications, such as urethral stricture and of the more florid secondary and tertiary skin lesions of syphilis, is due to the fact that, generally speaking, the African will only complain of a condition that is visibly obvious or painfully inconvenient.

GONORRHOEA

Gonorrhœa is ubiquitous in most parts of tropical Africa but is particularly prevalent in urban areas and in those localities where men are working away from their homes or where military forces are, or have been, stationed. A high proportion of the women in these areas are promiscuous and it is fairly certain that not far off one hundred per cent. of these are infected. In 1945, Bettley reported that examination of a large number of prostitutes at a military station in Kenya showed that 63 per cent. were gonococcus-positive on smear diagnosis alone. Although many of the sufferers of both sexes regard gonorrhœa as "an annoying variant of normality" (Willcox, 1946), it is an important public health problem, as in many areas salpingitis is a frequent cause of invalidism, and in Uganda the number of patients admitted to hospital for retention of urine due to urethral stricture is surprisingly high. In most of the latter cases excision of the stricture is the only practicable treatment, as so many of the patients live too far away from the hospital to attend regularly for gradual dilatation. I could find no satisfactory reason for this high incidence of stricture in Uganda. An obvious explanation would be the local instillation of caustic drugs, but there was no evidence that this was ever practised. Gonorrhœa has for many years been common among the Masai, a once war-like tribe of nomadic cattle ranchers on the central Kenya plains. The disease is fast destroying this people, their rapid decrease in numbers being attributed largely to salpingitis among their womenfolk. Incidentally, they are one of the few peoples in East Africa whose tribal customs allow for a certain amount of promiscuity, a visiting traveller of the same tribe being provided with the comforts of both bed and board by his hospitable hosts.

SYPHILIS

Syphilis is extremely common throughout the length and breadth of detribalized tropical Africa and it is now rapidly penetrating the tribal areas, being carried there by workers returning to their homes after a spell of work in towns or settled areas. In many of these localities native families are not permitted, and prostitution is consequently rife. The long incubation period of the disease makes early detection of infection in these returning workers practically impossible, a fact which will be appreciated by venereologists here at home, who have seen a similar importation of syphilis by returning Service men from Germany and other overseas areas.

The coexistence of *yaws* has made the diagnosis of syphilis a doubly difficult business, as serum tests are equally positive in both diseases and the *Spirochaeta pertenuis* is indistinguishable from the *Treponema pallidum*. Nevertheless, to the experienced observer, the clinical differentiation of the primary and secondary lesions of both diseases usually presents little difficulty and it is only in the tertiary and latent stages that it is often impossible to distinguish one from the other. Even then, the typical scars of early yaws and the history of skin lesions in childhood will indicate the probable diagnosis, although here it should be remembered that a previously untreated attack of yaws confers no immunity against a subsequent syphilitic infection. This has been suggested by Findlay and Willcox, who in 1945 on the Gold Coast successfully inoculated with primary syphilis a man whom one of them had treated for yaws some years previously and whose blood test was positive at the time of the inoculation. This experiment, however, would have been more convincing had the yaws not been treated previously, as it is now known that even a second infection of syphilis can be acquired a few days after penicillin treatment of the first infection, even while the blood tests are still strongly positive.

It has often been said that syphilis in the tropics is largely a dermatrophic infection and that invasion of the cardiovascular and nervous systems is relatively uncommon. Whilst the number of patients coming for treatment with tabes, dementia paralytica and cardiovascular syphilis is small compared with those showing skin lesions, it must again be remembered that the primitive African will usually only complain of signs that he can see or of symptoms that hurt. His average life span is far shorter than that of the European, and the candidate for late syphilis of the vital systems will only too often die of an intercurrent disease long before these conditions will force him to seek treatment. Although it has been suggested that endemic malaria may play some part in the prevention of neurosyphilis, it seems that induced malaria is of little curative value in Africans with dementia paralytica. It is interesting to note that Muwazi, Trowell and Davies (1947) state that syphilis is the cause of 30 per cent. of all cases of insanity at Mulago Hospital, Kampala, and it is apparent that meningovascular syphilis is by no means uncommon. I was impressed by the number of epileptics

being treated for burns after having fallen into open fires, and it seemed unlikely that in all these cases the condition was idiopathic. Davies (1947), the pathologist at Mulago Hospital, reports that in two large series of necropsies, evidence of syphilis of the vital systems appears in a fair proportion of the total, and it is significant that in the smaller, more recent, series this proportion has appreciably increased (table 1).

TABLE 1

	Series 1 2994	Series 2 460
Total necropsies		
Total cases showing evidence of syphilis	338 (11.2 per cent.)	75 (16 per cent.)
Syphilitic aortitis	207 (61.2 per cent. of syphilis)	48 (64 per cent.)
Neurosyphilis	154 (44.5 per cent. of syphilis)	36 (48 per cent.)

Although in a survey made before the 1914-18 war, Lambkin and Keane (Keane, 1912) considered that syphilis was even then a common disease in Uganda, it is now thought that many of the cases noted were in fact those of yaws and that the dissemination of syphilis in that country did not take place until well on in the inter-war period. If this is the case, the disease is still "young" in Uganda, as it is in many parts of Kenya (Carothers, 1948), and the amount of cardiovascular and nervous complications may be expected to increase, especially in view of the great rise in the incidence of early syphilis which took place in all parts of East Africa during the recent war.

It is a strange and so far inexplicable paradox that, whereas the number of untreated and insufficiently treated cases of early syphilis is high, the incidence of *congenital syphilis* seems to be extremely low. Nevertheless, abortion is common and it is possible that, for some reason yet unknown, the infected foetus may rarely reach maturity. It is also possible that syphilis is often acquired early in adolescence and becomes relatively quiescent during the childbearing years of life. Be this as it may, both classical infantile congenital syphilis and later manifestations such as interstitial keratitis, nerve deafness, and Hutchinson's teeth are hardly ever seen. Periostitis of the long bones is a common manifestation of yaws in children; it is by itself almost indistinguishable from the similar syphilitic condition, but confirmatory evidence of yaws is almost invariably present in these patients.

Despite the fact that *lymphogranuloma venereum* (lymphogranuloma inguinale) is met with throughout Kenya and Uganda, and I saw several female cases with rectal strictures in Mulago hospital, the disease does not at present seem to be a considerable public health problem and in its early stages responds well to sulphonamide treatment. Granuloma inguinale (granuloma venereum) is also seen, but still seems to be a rare disease. It is

SYPHILIS

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better advantage in this direction rather than in the casual treatment of the promiscuous male.

Such a plan presupposes a social service, and no clinic or mobile team will be complete without its African male and female social workers, whose chief rôle will be the tracing of contacts and the bringing of them to the clinic. With modern rapid methods of treatment, case finding is all important and the public health value of case holding of but secondary significance.

The African loves an intravenous injection, and it is in this sense unfortunate that penicillin has to be administered by the intramuscular route. The tremendous reputation of the arsenicals in yaws and the fact that the patient can taste them a few seconds after they are given, have convinced him that this is indeed strong medicine, and powerful propaganda will be needed to persuade him that the new agent is superior to the old. In addition, the intravenous arsenicals have acquired a reputation as a panacea, with a special bearing on sexual potency, and some unscrupulous practitioners have pandered to this superstition by selling single injections for comparatively high fees. The fallacy that the best goods are only to be obtained in the black market dies hard in Africa, as it does at home, and the excellence of free treatment is still doubted in many quarters.

CONCLUSION

My personal experience of tropical Africa is limited to two years' service as a combatant in the first world war and a two months' tour of Kenya, Uganda and British Somaliland as one of the Nuffield medical visitors in the summer of 1948. It was thus with some diffidence that I accepted the Editors' invitation to write this short article, with the knowledge that there are many who must know more about the subject than I can possibly do myself. To these I acknowledge, in all humility, my comparative ignorance, and in conclusion would thank the many medical officers in the three colonies, not forgetting their Directors of Medical Services, the medical missionaries and the private practitioners who so generously found time to show me so much, to discuss this problem with me, and with so many of whose opinions I am in such complete agreement.

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CONTROL MEASURES

How then is the solution of this problem to be found? Leaving aside for the moment the all-important social side of the question, without regard for which any purely medical measures are foredoomed to failure, the answer is, I think, the intelligent use of *penicillin*. It is already known that an overwhelming majority of all cases of gonorrhœa can now be cured in one day by this agent and that most cases of early syphilis can be made non-infective and probably cured in a week. In penicillin we have a therapy that is, from the public health point of view, completed before the disappearance of signs and symptoms, and which is consequently ideal for the African patient, who is ever prone to early default. Very large amounts of this still costly drug will be needed, and it must never be forgotten that if female sexual partners are not sought, found and simultaneously treated, it is waste of time and money to treat the men. For a start, the problem of prostitution in the towns and settled areas will have to be tackled and rigid legislation against this evil enacted and enforced. If this is to be done effectively, it surely follows that a progressive policy of housing the wives and families of workers in these areas, and consequently of encouraging family life, the greatest enemy of venereal disease, should be begun as soon as possible. The administrative, financial and political implications of such a policy are, of course, far reaching if not revolutionary, and even with the best will in the world its implementation would be bound to be slow. Meanwhile, much can be done to prevent the spread of infection by the inauguration of an intensive propaganda campaign accompanying the provision of facilities for rapid diagnosis and treatment in town and country, and it is good to learn that, in spite of a grave shortage of doctors in these colonies, both Kenya and Uganda are appointing specialist venereal disease control officers for their territories.

In hyperendemic rural areas, mobile teams with dark field microscopes and adequate supplies of penicillin, preferably in a slow release vehicle, should systematically comb the countryside, treating all cases which are clinically suspicious as well as those which are proved microscopically. Although a rapid screen test, such as Laughlen's precipitation test, could be done on the spot in doubtful cases, the accent should be on microscopic and clinical diagnosis rather than on serological findings. The hidden nature of both diseases in women should be stressed and the risk of sterility as the result of infection broadcast to all. This should be a trump propaganda card in Africa, where even prostitutes accept pregnancy with pride and pleasure. The reservoir of infection of both diseases lies in the untreated female, and such supplies of penicillin as are available will be used to

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much more certain in young campers than in striving athletes, about whom he was writing.

SUNBURN

By far the most common disability campers suffer from, even in this country, is the result of sunlight, often ably assisted by wind and salt water, irritating areas of their skin which are habituated to urban gloom or civilized clothing. It can be serious in the sense that it prevents a person from enjoying his short annual holiday, but against this it must be remembered that although the patient may have been confined to his tent or the shade with painful blistered shoulders or peeling chest or œdematous legs, his leucocytes have had a glorious outing.

Sunburn may also be serious in a very real sense. Hope Gosse recorded eleven cases of pulmonary tuberculosis of the exudative type in young people which had apparently been activated or reactivated by sunbathing in the hot summer and autumn of 1933. Sanatorium doctors demand great caution from their patients in exposing themselves to direct sunlight. How it acts nobody seems to know, but probably like thyroid extract, which can be lethal to the tuberculous, by raising metabolism and breaking down the barricades round the beach-head where the tubercle has lodged. Or it may be that the vasodilator substance which causes the erythema of sunburn is the reactivator; at any rate the prolonged exposure by phthisical patients is often followed in an hour or two by hæmoptysis. So far as camping is concerned any boy or girl whose parent is in a sanatorium, any contact, might well be warned against excessive sunbathing or, better still, advised to tan gradually in a series of week-end camps. Many sanatorium doctors believe, and I am fanatically with them, that sunlight in carefully graduated and increasing doses in time and area is of immense value in pulmonary tuberculosis, and provides some necessity for the full circle of health.

In my experience sunburn is more common in this country in the East and South-East coastal areas, the so-called "dry belt". At the Duke of York's Camp, which was held in these areas and was a vigorous affair, almost everybody in some years got some degree of sunburn, the backs of the knees and shoulders being the most painful sites, so much so that I had more cases of sunburn there than I ever had in ships lolling in the tropics. Sunburn is looked on as a trivial, indeed a laughable complaint, but as it is so common and spoils so many holidays, and as on rare occasions it is only the superficial sign of deeper troubles—sunstroke, heatstroke, and reactivated tuberculosis—it is worth while trying to get some clear views about it.

The events that follow the exposure of untanned skin to the sunburn spectrum of ultra-violet radiation are:—

- (1) Erythema restricted to the area exposed and appearing in an hour or so.
- (2) Œdema, barely perceptible except with prolonged exposure, and reaching its maximum on the second day.

THE MEDICAL HAZARDS OF CAMPING*

By C. G. LEAROYD, M.R.C.S., L.R.C.P.

THE enormous growth of camping in the last forty years in this country owes much to Baden-Powell's paternal urge to share with his young countrymen the good things he had gathered in a life of campaigning, something to improved communications, and a great deal, and more fundamentally, or so it seems to the biological eye, to the dire necessity for the young mammal man to escape for a time from the stunting and constricting conditions of urban and industrial life and go back in some degree to those in which for countless centuries his body and mind were fashioned and nearly fixed. Any cluster of youngsters with bikes and a tent have one of the fairest playgrounds in the world, the more skilled in camping they are the farther afield they can go; a real adept can be cosy on an iceberg. They stream out of the cities in their hundreds every week-end, and in their thousands at the times of the feasts.

Now these young people when camping are in healthier conditions than when at home or at work or at school; the hazards they run are of the traumatic sort: pricks, stings, cuts, losing bits of their hide on hedges or the good earth, assaults on their skins by the elements, to combat all of which they have ample natural defences. The strategy of these defences—the leucocytosis, the antibody and pus and pigment formation, the cautionary instinct—was laid down millions of years ago; occasionally we doctors, counsellors in every home, are asked to advise on tactics.

From the more serious medical conditions campers are comparatively immune; in forty years I have seen remarkably few and these occurred in the first few days, that is to say they originated at home. I have never seen a case of pneumonia originating in camp and this condition is rare in sanatoria also, which may be regarded as medical camps. There was never a case of ordinary pneumonia at Frimley Sanatorium, at any rate in its first fourteen years. Many a scout camp has gone on year after year without having to call in a doctor; two troops to my knowledge for over twenty years. I do not believe that damp blankets, occasional lack of groundsheets, and cold sleeping, although uncomfortable and undesirable, do any harm, but it is the instinct of mothers to attribute all subsequent disasters to them. Nor do I believe that over-exertion, inseparable from some hikes and some long camping days, ever does harm to the fit. Clifford Albutt said that "in his experience not a single instance of permanent harm from exercise had ever occurred in young men except after some infectious illness such as influenza", and the automatic closure on activity by feelings of laziness is

* Reprints of this article in pamphlet form are available on application. For further particulars see page 436.

at 2s. a pound is a cheap and efficient substitute. At the Duke of York's Camp we used a 1 per cent. solution of picric acid which the campers painted on themselves and when this was dry they smeared over with yellow petroleum jelly. This was effective as a preventive and sedative, but there is a risk of dermatitis, although we encountered only one case in hundreds. Although some people object to going about with yellow legs like lesser black-backed gulls, there was no objection amongst these lads; indeed some dormant skin-daubing instinct seemed to be revived. Acriflavine emulsion, especially if there are raw areas, is better in every way. One action of picric, of course, is to coagulate protein, and this effect may be obtained with surgical spirit; this followed by coconut oil was once popular on the Sydney beaches. Gall is useful for the same purpose and some of the proprietary preparations for the prevention and treatment of sunburn depend upon it. A typical formula is:—

Tincture of gall	5.0
Menthol.....	0.25
Phenol	0.5
Glycerin	3.0
Salicylic acid	1.0
Water and alcohol	to 100

A 10 per cent. cream of salol, made by dissolving the salol in a minimum amount of liquid paraffin and mixing the solution with a base of cold cream, is said to be an effective application for the absorption of ultra-violet rays. The horse chestnut provides a glucoside, called "æsculin", 2 per cent. of which in soft paraffin is said to be useful.

TENDERFOOT'S SYNDROME

This is an indefinite form of malaise that sometimes attacks young campers about the fourth day of camp when the early exuberance which exposed the patient to too much sun, too much and too peculiar food, and overactivity receives a check. The boy or girl feels drowsy, has a temperature of 100° to 101° F. (37.8° to 38.3° C.), and if he or she has managed to retain the tonsils they are enlarged. But then in my experience tonsils in young people are always enlarged with any disturbance of their thermality, with successful vaccination, with any inoculation that produces fever, and with prolonged seasickness. Tonsils are like the guardian geese, who no doubt squawked exceedingly if attacked *qua* goose, but far more often from apprehensiveness. There is generally constipation, and with a cheerful dose of bubbling salts and shaded rest the condition clears up in twenty-four hours, leaving a slightly subdued and wiser camper.

Appendicitis does not seem more common in camp than elsewhere, which is odd considering the trials the gut as a whole undergoes with camp cooking and other delights.

(3) Erythema flare, extending irregularly from the exposed area, usually appearing about the second day and only after heavy doses.

(4) Desquamation, varying from flaking, which occurs after several days, to blistering, which occurs earlier.

(5) Pigment formation after several days, the pigment coming from the hæmoglobin of the dilated vessels and the melanin of the skin.

(6) Darkening of the pigment, which is caused by the longer wave-lengths of the sunburn spectrum.

The way these effects are probably produced are: (1) There is essentially only one type of photochemical process involved, an alteration of the protein contents of the living cell. (2) The response to this damage is the elaboration of a dilator substance which travels to the superficial minute vessels of the papillary layer, releases them from the hormonal or nervous mechanism that keeps them constricted, dilates the vessels and manifests itself grossly as erythema. The curious thing is that the longer ultra-violet radiations of the sunburn spectrum, or some of them, the ones that penetrate to the papillary layer, have an inhibitory effect on the erythema formation, that is to say, there is a qualitative as well as a quantitative form of sunburn, and that is why the degree of ultimate trauma sometimes seems out of proportion to the degree of erythema. The mechanism of the inhibition of erythema by these longer wave-lengths is not known, but a naturalist would suspect that the organism has learnt that these longer waves are of value to it and must not be stopped altogether.

As so often happens in the scientific world, having been led up an interesting garden path, there is nothing very solid at the end of it. Here is the summary at the end of an article, entitled "Evaluation of Protective Measures Against Sunburn" (Blum, Eicher and Terus, *Amer. J. Physiol.*, 1946, 146, 118):

This paper presents the studies undertaken to determine the degree of protection against sunburn afforded by various preventive preparations with the primary aim of selecting those most effective for use under severe conditions. It was found that the degree of protection afforded against sunlight and other polychromatic radiation by a sunburn preventive is a function of a number of variables, including the spectral distribution of the radiation, the transmission spectrum of the preventive and the numerous factors affecting the threshold of the subject. Wide differences in the estimation of the protection afforded by sunburn preventives are obtained by different methods and may lead to erroneous conclusions. The authors summarize by stating that individual estimates of the value of preventives may be widely divergent.

So one comes back to the folklore of one's own experience. Of course, the commonsense of the matter is to disrobe gradually and tan gradually; discard not the long funereal trousers and sleeves of civilization too hastily or for too long. But you are not going to get much cautious restraint in the exuberance of sudden release from city and clothing.

The nicest *preventives* are the vegetable oils, coconut and olive oil, which "superimpose another absorber of ultra-violet light on the corneum" (and on the sebum, one might add) and are also emollient. Soft yellow paraffin

protection of food from flies and the protection of flies from faeces. Drinking water may be of dubious purity on the outskirts of civilization and it is a fallacy to suppose that because inhabitants have been drinking a water for years it is bacteriologically safe. There have been several cases where campers have suffered from an enteritis from drinking water to which its regular drinkers were immune. Unfortunately it costs two or three guineas to get water tested, a big sum for a small troop. Under the Public Health Act 1936 there is no specific provision whereby a person or body conducting a camp may have a putative drinking water tested free of charge. Human sewage contamination is the danger in this country; in the sheep country of New Zealand and Australia dog faeces brings the hazard of the hydatid. Swimming water too may be contaminated by other people's intestinal and nasopharyngeal fauna and flora, but this is far more likely in swimming pools and in the baths of towns. There have been a number of cases of mastoiditis and ethmoiditis, some of them fatal, from this mode of infection. Man is essentially a terrestrial animal; under water he is much inferior to the alligator who can close his nostrils by sphincteric action. It is not fussy to exclude children with running ears from swimming in pools, both from their own and their friends' points of view.

DROWNING

As most camps are by water, salt or fresh, and as deaths of campers by drowning take place every year and are nearly always preventable, the problem of prevention is, or should be, ever present in the minds of those who camp or run camps. Not only is a young life lost and the light gone from some home for ever, but the happy, healthy and restoring practice of camping is damned in the eyes of many by one of these tragedies. It is worth space therefore to make a brief analysis of the matter. The problem, like that of road casualties, is largely a psychological one, using that word in no culted sense. Children and young people, so much wiser than some psychologists, love and are hungry for horror stories. It is not primarily morbid or ghoulish; it is the natural way they learn of the dangers that beset them, a learning from vicarious experience.

When I was a youth there was a sailing accident some way from where I lived, in which five boys were drowned. I was naturally avid for details, gleaned second or third hand from people who recovered the bodies or from witnesses at the inquest. It gripped my imagination with awe until it was very satisfactorily topped off with a moral; the man in charge of the boat "had tied the sheet", a crime in small boat sailing, a sin against the gusts that is sometimes not forgiven. Since then "Thou shalt not tie the sheet" has been engraven on my mind more deeply than some of the Ten Commandments.

This is the natural way the human young learn and the apprehensiveness, as in an exciting story, is maintained until a satisfactory moral or explanation is reached or fabricated. The justice of little Tommy being eaten by the lion because he stole the honey is accepted by the child and adolescent

ALLERGIES AND SUCH

Camp is essentially a place of new experiences, physical and mental, and probably the two are much more intimately connected than is realized. A naturalist will look on a camp as a place where the human organism meets new foes and foods, conquers them or is conquered by them, or breaks off battle when he returns home. There is an enormous amount of variation in the individual response to certain enemies and foods. Some boys will react violently to certain mosquitoes, others will not react at all, as though they had not been pierced by proboscis. The same boys will be attacked year after year by harvest bugs, which are more common in inland camps. A 5 per cent. sulphur in talcum powder dusted on the stockings will discourage this six-legged larval form of acarid, petrol will detach him, and those to whom he is particularly addicted should carry benzocaine, 2 g. in 15 ml. of flexile collodion, in a rod-stoppered bottle to allay the itch. Most are not attacked; so far as I know I have never been bitten.

I gained the impression that it is the fair boy or girl who reacts most violently to the attack of gnat, flea or harvest bug and the sting of bee, wasp or nettle, and to the new food, which at first was a puzzling observation; but that when they are well tanned and weathered they are the toughest of the lot, which seems to make sense.

At a boys' camp with which I was associated for eight years there was an abundant supply of cockles and I saw most of the stages of man's conquest of the cockle as a food: a few were nauseated by the sight of them, a few vomited them, to some they gave diarrhoea, to half a dozen skin rashes, urticarial or rather like chickenpox, but the majority ate bucketsful with relish. Who knows what correlated qualities, what marine desires and oceanic longings are formed by the conquest of the cockle? An absolutely unexplored field.

During a two months' camp on Lake Taupo a friend and I almost lived on the lovely red, oil-oozing flesh of the rainbow trout. At first we delighted in it, then we got tired of it, then it nauseated us, then we got used to it, and when we left we hankered after it. Something had happened to our inner chemistry which had made us able to live on trout, a feat which in conceivable circumstances could have a survival value. Twenty years later even a bit of smoked salmon will bring back the sound of the shrieking reel, the arched and vibrant rod, the New Zealand sounds and sights and smells more vividly than any straining of memory. On the other hand, I was earlier completely defeated by bracken, the young shoots of which I fried in olive oil. I vomited on and off for days, and for months the sight of a ferny landscape or even the printed word "bracken" brought loathing. Others have had the same experience with samphire, for which I craved in season.

Some very strange foods are eaten by boys in camp, apart from the new mixtures of amino-acids and cinders that are apt to result from the vagaries of camp cooking. The new food or possibly the same food cooked in a different way may cause difficulty in assimilation and may be the reason why Scout troops visiting Eire and Northern Ireland seem to get a number of abdominal complaints which, however, pass off with exercise.

HYGIENE AND ALL THAT

Among the few things it is worth while being incisive about in camp is the

most of them initially non-swimmers, holding its two swimming parades a day on an estuary which had a five-knot current at spring tides, went on for year after year and never had anyone even half drowned. But that one rule certainly wouldn't be deemed to provide the proper margin of safety to-day. The picket of good swimmers, the life-saving rope, the vigilance of the bird in the field, the local knowledge of the water, its currents and caprices, the rigid rules for boating that provide safety with a good margin, these should be the expressions of alertness in those in charge of other people's children. "This cannot happen to me"; "After all very few people do get drowned"; "We don't want these gruesome suggestions hovering over a happy camp": those are the dangerous frames of mind. The Boy Scouts Association's rules and regulations for swimming and boating are a model of carefulness, experience and sense of responsibility. Some may seem fussy, e.g., the rule which says that the first-class swimmers who watch the others swimming before they themselves swim shall while so watching wear great coats. I mention this because although I had served at sea for a number of years and had seen some drowned people, a few very drowned, it was the breach of this rule that gave me my only experience of meeting the apparently drowned.

We were out at sea in a sailing dinghy, when a boy looking through the glasses said, "They are doing artificial respiration on the beach". A lad of seventeen, a first-class swimmer and life-saver had been on watch while the others swam, wearing only a mackintosh over his slips, and it was a cold day. When they had finished, he had rowed the dinghy about thirty yards from the shore, anchored it, dived off, got cramp and was eventually pulled out. The prolonged wait, the cold, the insufficient covering, the cramp—that seemed to be the logical sequence. When we got there he wasn't breathing, his lips were black and his face a paper-white. He looked profoundly, irrevocably dead. I wonder if the Red Cross books emphasize this enough. I lifted him up by his hips, and some water, possibly six ounces, came from his bronchial tree. A team got to work on him; some lay on their bellies and stroked the blood up his veins, some fetched heat in water and rugs to conserve it, while the arms of the strong in relays forced the stagnant air from the carcase in rhythm. Years before I had visualized something of this sort and had asked a distinguished pharmacologist what was the best stimulant to inject into the apparently drowned. He said "A combination of adrenaline and posterior pituitary into the heart muscle". I therefore always carried it and injected it on this occasion. It certainly would not be recommended to-day. A recent appeal by case stated to that most helpful of High Courts, the Medical Research Council, brought this from one of their experts:

"I think the answer to the enquiry about the apparently drowned is that it is certainly desirable to stimulate the respiration. The most effective way of doing this is the administration of a mixture of oxygen with 5-7 per cent. of CO₂. This should be effective. The injection of a respiratory stimulant is also likely to be helpful. Injections of pituitary are not indicated. Injections of strychnine are not likely to be very effective. Injections of alcohol act only by the local effect of the pain which they cause, which acts reflexly; they are not very effective. The best drugs to use are either nikethamide (coramine) or leptazol (cardiazol, metrazol). The first of these drugs is probably the most popular in this country, but the pharmacological evidence which includes direct clinical comparisons is in favour of leptazol".

However, the lad started to breathe in about four minutes, that is to say we stopped artificial respiration and he gave a few unconvincing intakes, so we went on and later they became deeper. I had never realized before how waterlogged the

mind—as with characters in the Old Testament, it is an extension to the moral sphere of the intense human desire to get an explanation of disasters so as to be able to avoid them. “How to drown yourself” was always a popular little talk, although like most vital information its message reaches a deeper consciousness in anecdotal form or as an aside. The current that carries away obliquely like some wicked abductor, the undertow that drags down like a giant octopus, the cramp that comes from long coldness before swimming, the unconsciousness of the current when you’re swimming with it, these things should be known to all. A camper on the Broads is safer if he knows that people have been drowned by getting entangled in weeds, especially *Potamogeton natans* with its cord-like stems, and by diving from a boat in too shallow water and getting stuck in the mud. For all such succulent details the mind of youth is hungry and I doubt whether he ever forgets. So much more swimming and boating can take place if the real dangers are known and guarded against, just as the platelayer can saunter jauntily down the electric railway because he knows where the live rail is.

The mental attitude that is the most common preliminary to a drowning tragedy is the bather’s desire to show off boldness or prowess in swimming before his fellows, by going out too far or in too rough a sea, rather like the sexual display of drakes. Often the person drowned is not the display, but someone who has to try and rescue him. As a rule a young person respects deep water as healthily as any other potentially lethal condition and is safe if left on his own; it is the presence of his or her comrades, the gallery, that incites. This display is, of course, by no means confined to aquatics, it is one of the motives for excellence in games, dress, the arts, and most other forms of activity, and humanity owes a great deal to it. It often accounts for the drowning of a good swimmer. The exposition of this thesis to young people lends itself to humorous treatment. The aversions from the namby-pamby, the emasculated, from rules and regulations, all are other aspects of this instinct for display; it is an amateurish attitude; the professional sailor has a most profound respect for the sea and the sudden things it can do.

Then in the case of boys or girls camping with someone in charge of them we have to consider the attitude of mind of those in charge:

“I’ll take the boys swimming”, said a curate in Queensland. “I don’t mind the surf and the sharks”.

“Unless you’re scared stiff of both of them you’re not going to take my boys swimming”, said the experienced scoutmaster.

A holiday camp for Hoxton boys with which I was associated forty years ago had one adamant rule: no boy can bathe or go into a boat unless there is an officer in charge. They were told this before leaving and at the first meal. One boy on the day of arrival in the exuberance of his wonderful new surroundings did clamber into a moored boat; he went home in tears and the next train. That camp, giving a fortnight’s holiday to a hundred boys,

MEDICAL SERVICES IN THE SMALL FACTORY

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THE importance of an efficient medical service for industry has been recognized for many years, and the majority of large firms are fully alive to the value of the services which medicine can offer to them. In order to meet the special needs of big firms, the study of occupational health has reached the status of a medical specialty, and recognized Diplomas in the subject have now been established. The plan of an efficient medical service for a large industrial works is now broadly developed and it has been found that, as a general rule, a firm employing 3000 or more persons can maintain with profit a full-time works doctor. Yet, in point of fact, most people work in factories employing 500 or less. Medical supervision in these establishments presupposes the attendance of a part-time doctor. Many firms, too small to carry a full-time doctor, have appointed a State Registered or a partially trained nurse.

In the future, general practitioners will probably be called upon more and more to supervise the health of industrial workers. The object of this article is to indicate the duties and responsibilities of a part-time doctor in a small firm.

THE WORK OF THE DOCTOR AND NURSE IN INDUSTRY

The duties of a works doctor fall into two categories. The first is to maintain a casualty service for the treatment of illness and accidental injuries arising at work. The second is to advise both employers and workers, particularly the former, on ways and means whereby hazards to health, arising out of the conditions of work, can be minimized, and on general measures to promote the health of workers. These duties have been set out in a memorandum drawn up by the British Medical Association in 1937, which also includes ethical rules for the industrial medical officer. These duties may be summarized as follows:—

(1) Examination of applicants for employment and advice as to their selection and placement.

(2) Examination and supervision of workers returning to work after illness or accident, whether of industrial origin or not, including rehabilitation at the place of work.

(3) Periodic examination of workers exposed to special hazards.

(4) Responsibility for the efficiency of the nursing and first-aid services.

(5) Advice to the management regarding: (a) the hygiene of the factory; (b) the occurrence and risks of dangerous hazards; (c) the accident-prevention arrangements; (d) factory legislation concerning health and safety.

drowned are. Apart from the water that came from his mouth he had a big, splashy vomit while being carried back to the camp, another in the hut on arrival, had many liquid stools in the next few hours and passed pints of urine. That night while he was sleeping his breathing several times became irregular, stopping for quite long periods as in Cheyne-Stokes respiration; the respiratory centre fighting its battles over again, as a dog's does chasing ghostly rabbits in sleep. He had some slight middle-ear trouble next day, a few scratches on the breast from the shingle and our vigour, but swam again on the third day.

This matter of drowning is dwelt on not because it is common or likely to be met with by many, but because it is a way in which some camps are every year ruined in ten minutes. Regulations, constant vigilance, incessant life-saving practice and swimming in clothes, and discipline seem but petty premiums to pay when one contemplates a young corpse on a slab.

THE HARVEST

When one sees repeatedly what an amazing difference two or three weeks camp can make to a city child or adolescent one is driven to the vegetable world for a parallel—plants deprived of light or water—and one is tempted to speculate on the causes. They have become robust and more self-confident, sometimes to the extent of becoming almost different beings; like those who have at last come into their birthright and heritage. No doubt the change is partly due to the physical impact of a new world; they have met new enemies, insects, plants and bacteria and pollens, they have struggled with new foods and samplings of foods, they have been more oxygenated and active, they may have suffered the autohæmotherapy of a bruise or two and absorbed salts through unusual channels, and in them for twenty or so long child-days that old autocrat, the skin, rescued from nonentity, has had a chance to play his ancient rôle. But besides these passivities, sometimes in response to them, there has been in almost every child-minute a new sensory experience or excursion: the smell of wood smoke which evokes different emotions according to concentration—a sweet nostalgia in, say, one in ten million, a fraternal fierceness in heavy concentrations round the fire; the far view of the mysterious ships on the horizon and the near view of the huddled fly caught on the sticky hairs of the sundew; the call of the redshank coming over the marshes and the crackle of hay in the pillow; the meeting with primal things, dawn and the dew on long grass that wets to the knees, sunset and the terror that comes from wide darkness alone.

I have noticed that men with whom I camped forty years ago still have particularly vivid recollections of those camps, by no means always recollections of comfortable times; oases of memory in the desert of forgotten things. About such evergreen memories surely we may exclaim as the bishop did about the old brandy: "Are not such things also worthy to be numbered among the therapeutics!"

denying her an opportunity to play her full part in the planning and maintenance of a constructive health programme.

PLANNING AND EQUIPPING A WORKS SURGERY

A works surgery exists for the purpose of providing first aid for all medical and surgical emergencies. A further function is the daily treatment of minor injuries and infections which do not disable the patient from working. It should also provide accommodation for individual consultations with the nurse or medical officer. It is no part of the service of a works surgery to treat chronic ailments or to provide medicine and drugs for domiciliary treatment.

In small factories accommodation is often of a makeshift nature, but so far as possible the surgery building should be centrally placed and accessible, free from undue noise and smells, well lit, and supplied with hot and cold water and drains. There must be easy access for stretchers and an ambulance. The surgery should be a separate building and not incorporated in one of the workshops. Ideally, it should provide a waiting room, a main dressing-room, a small consulting room, and a separate lavatory. In larger factories it is advisable to add a clerk's office and a recovery room, and where ancillary services, for example chiropody, are supplied, further accommodation will be necessary. It is realized that ideal conditions are often impracticable, but good work can be done in makeshift quarters. Internal fittings and furniture should be kept as simple as possible. Windows should be of the hopper variety to exclude draughts and dust, and the lower panes should be frosted. They must be large and kept clean. Floors and walls should be capable of easy cleaning and therefore impervious surfaces and rounded corners are recommended.

Surgical equipment.—The equipment required is shown in table 1. This equipment can be purchased to-day for about £200, and is sufficient for a factory of 500 to 2000 workers employing a full-time nurse. This may seem a great deal of money for a small firm to pay out, but these are not expendable stores and this capital expenditure should prove a good investment for many years.

To this must be added the cost of *drugs and dressings*. A multiplicity of drugs is unnecessary, and it is best to rely on a few remedies, the use of which is fully understood by the nurse. Most dressings in a factory surgery are small, as most works injuries are minor in character. An aseptic technique is desirable, and this demands sterile dressings and instruments and the proper training of nursing staff in "no-touch" methods. Drums are needed to hold gauze squares, lint and cotton-wool and, if there is no autoclave available in the factory, arrangements can usually be made to have these sterilized at a local hospital. Adhesive plaster and small occlusive dressings should be provided liberally for those working in wet or oily processes, and plaster is less liable than bandages to catch in machinery.

(6) The medical supervision of canteens to ensure the cleanliness, good quality, and physiological adequacy of the food.

(7) The promotion of educational work in respect of the health and fitness of the workers.

The ethical rules centre round the principle that the industrial officer is concerned with first-aid and emergency measures, but not with subsequent diagnosis and treatment. Following satisfactory first aid, the worker should be referred to his private doctor, except when he is sent straight from work to hospital: then the doctor must be informed at the earliest opportunity. If the medical officer considers specialist advice or hospital investigation is desirable, he may indicate this to the worker's own doctor, and in dealing with a case of suspected occupational disease he has a positive duty to place his specialized knowledge at the disposal of the general practitioner. When the works surgery is equipped to give regular treatment, such as daily dressings for minor lesions, these facilities should be offered to the patient's doctor; it is often in the interests of the patient himself that he be allowed to remain at work during treatment.

The doctor in industry is undertaking different functions from the general practitioner. His main duties lie in the preventive field. He is not primarily concerned with curative medicine. He is responsible for the supervision of the health of persons at their place of work, and to do this he must consider not only the individual worker, but the environment in which he works, and of the two, the latter is the more important because it requires specialist knowledge which he possesses but which is often unavailable to others. A healthy and safe environment with an intelligent selection and placing of workers and an efficient casualty service to deal with the cases of accident and illness, which can never be entirely eliminated, is the aim of a works medical service. The doctor who spends his time conducting general practice in a work's surgery is not only not fulfilling the duties for which he was appointed, but is encroaching on the functions of his professional colleagues.

The industrial nurse, who may hold the Industrial Nursing Certificate, should be responsible to the medical officer for her professional duties and not to the works manager. The Royal College of Nursing (1948) has issued sets of rules governing the duties, ethics and conditions of service of industrial nurses, comparable with those drawn up for doctors by the British Medical Association. It has been suggested that all nurses in industry should be under the supervision of a doctor, and one of the most important duties of the part-time doctor is to stimulate and maintain the professional efficiency and interest of the full-time nurse. All too often nurses in industry are working in isolated conditions, out of touch with their own or the medical profession, unable to keep up-to-date, lacking the stimulus of critical appraisal of their work and often having to submit to indifferent conditions of employment through the absence of a responsible person to watch over their interests. Some employers fail to make the best use of their industrial nurse by not giving her the status to which she is entitled and

firm "A" demands a sick certificate after a single day's illness, and firm "B" only requires one after three days, the term "certified sickness" will have a different meaning in the two organizations and the figures will not be comparable. Again, there is no general definition of the term "sickness rate", and this can be expressed in a number of ways which are non-comparable.

The purpose of keeping records is two-fold. First, they are needed by the medical officer for the performance of his professional duties in regard to the individual worker; secondly, they are required for the over-all supervision of the working community, including the periodic presentation of reports to the management. It is the duty of the industrial medical officer to write a report of the health of the workers for the management at regular intervals. Usually an annual report will suffice, but in exceptional circumstances more frequent reports may be necessary. This report will give an account of the work of the surgery, a general statement of the industrial environment, a discussion on any prevalent diseases, and a summary of the general health of the workers. For this purpose a few figures are valuable. A general idea of the health of a factory can be obtained from the following indices:—

(1) Total absenteeism: the average number of workers absent from all causes on any one day per 100 persons employed.

(2) Sickness absenteeism: a similar figure for those absent on account of certified sickness.

(3) Industrial disease absenteeism: a similar figure for those absent on account of industrial disease.

(4) Accident absenteeism: a similar figure for those absent on account of accidents at work.

(5) The accident frequency rate: the number of lost-time accidents per 100,000 man-hours worked.

(6) The average daily attendances at the surgery.

These six indices can easily be obtained from records, which must be available in any works. Changes in these will reflect accurately the health of the factory.

Individual medical records are confidential documents and must not be allowed out of the hands of the medical and nursing staff. Nor must medical information regarding patients be divulged to factory officials except in certain special cases. Doctors do not need to be told this, but employers often do. It is the medical officer's duty to maintain the same degree of professional secrecy in a factory that he would in his own practice. There are only two exceptions to this rule:—

(1) When in the interests of the worker it is necessary that his employment be conditioned in any way, it is often advisable that his superior be told the reason. For example, a shop manager should know that one of his men is an epileptic and can only work in specified jobs. This information can be given with the consent of the worker, which is seldom withheld.

(2) Compensable disease and injury is a matter of immediate concern to

Boric lint has no place in the surgery and should not be available. Its presence on the dressing trolley is but an inducement to apply hot fomentations, than which there is no worse dressing for an industrial worker. The type of splints will depend upon the hazards of the job and the amount of medical attention provided. Fractures of the long bones are uncommon and it is the fingers and toes, and to a lesser degree the small bones of the hand and foot, which are chiefly involved. Full treatment of these injuries is not practicable with part-time supervision and therefore the splints provided will be for emergency use only. The provision of a Thomas' splint implies knowledge of how to use it by the first-aid staff, and it is therefore as well to have a long Liston splint in reserve. A back splint for severe foot injuries and the occasional Pott's fracture is also advisable.

TABLE I

	Scale No.		Scale No.
Examination couch	1	Surgery chair	1
Trolley	1	Bin for dirty dressings ..	1
Beds	2	Mattresses	2
Blankets	12	Pillows	4
Stretchers	2	Dressing drums—small, 10"	3
Foot bath	1	Arm bath	1
Electric cradle	1	Hot-water bottles	3
Enamel bowls 8"	6	Instrument tray	1
Kidney dishes	3	Pint measure	1
Medicine glasses	2	Undine	1
Glass jars with lid	6	Spatula	1
Tape measure	1	Thermometer—room ..	1
Thermometer—clinical ..	2	Syringe—car	1
Syringe—hypodermic 2 ml.	1	Syringe—hypodermic 10 ml.	1
Scissors—blunt	1	Scissors—pointed	1
Forceps—dressing	2	Forceps—sinus	1
Forceps—splinter	2	Forceps—Spencer Wells ..	2
Forceps—Cheatele	1	Probe	1
Scalpel	1	Cutting needles	6
Needle holder	1	Sutures	misc.
Camel-hair brush	1	Test tubes	12
Test tube rack	1	Spirit lamp	1
Electric torch	1	Instrument sterilizer ..	1
Weighing machine	1	Oxygen cylinder and stand ..	1
B.L.B. mask	1		

RECORDS

No conformity has been reached in the maintenance of medical records in industry and it is impracticable at present to lay down hard and fast rules as to their method of keeping. Nor is it often possible to compare industry with industry or even factory with factory. The chief difficulty is not only that records are incomplete, but different indices are used and the same definition may have several meanings in different firms. For example, if

THE EXAMINATION OF WORKERS

The examination of workers may be voluntary or statutory. The first includes *pre-employment examinations* which are not universal in this country, and are not easy to organize with only part-time medical supervision, nor are they often made a condition of employment. The part-time doctor, however, can make a point of seeing all newcomers as soon as possible after they have taken up employment, and disabled persons should invariably be medically examined before they are allowed to start work. Pre-employment examinations cannot be carried out satisfactorily without a knowledge of process and environment on the part of the doctor. This must include an appreciation of the physical and psychological requirements of the different jobs, together with an accurate knowledge of the potential health hazards.

The medical officer working part-time is not in a position to see all workers returning after sickness, nor is this necessary if a nurse is employed. He should supervise the sick list so that any abnormal incidence or serious case does not escape him. A worker may need a change of job following an illness and this will require a recommendation from the doctor. He should also give his nursing staff precise instructions regarding their duties in his absence, and he should insist to his employer that no worker is allowed to go off sick during working hours or to return to his job after illness without reference to the medical department. If this rule is not followed cases of works injury and industrial disease will be missed, sometimes with serious consequences to the patient.

The statutory examination of workers is not usually the duty of the industrial medical officer. Young persons up to the age of eighteen, entering factories for the first time, are required to be examined by the Appointed Factory Doctor for the area in which the factory is situated, and boys on night work and all those working in certain prescribed dangerous processes must submit themselves for periodic examination. Unless the industrial medical officer has been specially "appointed" by the Chief Inspector of Factories, these duties will not lie within his province.

GENERAL HYGIENE AND WELFARE

The medical officer must act in an advisory capacity to the managing director with regard to the general hygiene of the factory. In the environment of the worker there may be dangers arising from the use of machinery, the presence of toxic materials, and other factors which have a bearing on the health of the people. He is not required to attain the same specialized knowledge as the works engineer or works chemist, but he must learn sufficient of their tasks to be able to meet them on their own ground. To do this he must know the basic principles of heating, lighting and ventilation, and have some knowledge of such chemical processes as are carried on in the works. This is not so formidable as it sounds, and if the medical officer will take the

employers, and the medical officer must be prepared to give any relevant medical details which are necessary for the assessment of disability.

Divergencies arise over the recording of sickness among industrial workers. Report No. 85 of the Industrial Health Research Board ("The Recording of Sickness Absence in Industry", H.M.S.O., 1944) sets out in detail a method for recording all absences due to illness or injury. The sickness register, the basis of these records, may be kept either in the medical department or in the personnel office. The latter is preferable as day-to-day notifications of absence will be received there, but in all cases the periodic analyses must be made by the medical officer, and the doctors' sick certificates should be sent finally to the medical department for inclusion in the workers' individual records. Unfortunately, many sick certificates received by firms do not state the nature of the illness, and blank notes swelling the "miscellaneous" column do not make for a satisfactory analysis. This hesitancy on the part of private practitioners may be due to a suspicion that medical certificates are not treated as confidential documents inside the factory, but this is not so. Except when they have to be handled by a clerk for recording purposes, doctors' certificates and letters are invariably kept with the workers' personal records, and in the hands of a responsible person.

FIRST AID IN THE FACTORY

First aid should be done in the surgery and not in the workshops. Nothing is so conducive to a high rate of sepsis as the treatment of minor injuries by unskilled and dirty methods. The removal of foreign bodies from the eye by workers themselves is particularly to be deplored as damage can so easily be done. The medical officer starting a service will find that he has much training to do in regard to the immediate reporting of all injuries for treatment, no matter how trivial. First-aid cabinets are a statutory requirement under the Factories Act, but exemption may be granted by the District Inspector of Factories to a firm which maintains an ambulance room. This exemption must be officially applied for by the occupier, and the mere establishment of a surgery with a nurse or medical officer does not automatically relieve him of the duty to provide first-aid boxes. Some first-aid boxes may be kept in isolated corners of the works, especially those far away from the main dressing station, in canteens, where the risk of burns and scalds is high, and at night if people are working but the ambulance room is closed. These boxes should contain a supply of sterile wound dressings and nothing else. This will ensure adequate first aid, but will not be sufficient to exclude proper treatment at the factory surgery as soon as possible. In the case of night-shift workers, a few simple remedies and dressings may also be included, provided there is someone competent to apply them. In all cases when first aid is given in the factory, the patient must be seen by the nurse before he goes home.

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trouble to "learn his factory" when he is first appointed, he will quickly acquire all the knowledge he needs. Industrial medicine cannot be successfully practiced only in the works surgery, and the man who does not get out and about the factory will find the work boring to himself and unrewarding to his employer.

The medical officer should be notified well in advance of any proposed change in process, especially if this involves the use of toxic substances, the employment for the first time of women or young persons, or any substantial change in working hours, particularly if a shift system is to be introduced. Unless this is done, mistakes may be made involving risks to health or breaches of the law. For the same reasons the doctor should be acquainted with plans for new buildings or disposal of machinery within the workshops. If a Safety Officer is employed, it is his primary duty to ensure safe conditions for work, but the doctor must also be aware of any changes taking place, as his trained eye may appreciate hazards which are not immediately apparent to others.

A medical officer has no executive authority outside his own department, but he has a supervisory responsibility for cloakrooms, ablution rooms, lavatories and canteens. The proper management of canteens is still not always appreciated, and there is much ignorance regarding the principles underlying the provision of a safe food supply. Canteen workers should be inspected at intervals by doctor or nurse and must be taught the importance of reporting even minor symptoms of ill-health. The day-to-day preservation of food and the disposal of waste should be supervised by the medical officer, and he should also see that the meals provided are adequate and attractive.

LIAISON WITH OTHER DEPARTMENTS

The industrial medical officer is one of a team, all concerned with the health and safety of the workpeople. He must work in closest cooperation with the personnel manager and with the safety officer, and the establishment of good relations with these two will do much to oil the wheels of his job. He should be a full member of the safety, canteen and health committees, where they exist, and must also be prepared to attend joint production or Whitley committees when asked to do so.

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Many doctors entering industry are often at a loss to know where they can find information which will help them in their new work. We have therefore appended a list of useful publications. The list is divided into three parts: (1) those which all industrial medical officers should possess; (2) those to which reference should be made for specific information on various subjects; and (3) textbooks and journals on industrial medicine and allied subjects.

(1) *Essential Publications*

- Factories Acts 1937 and 1948. (When the doctor is to be employed in another type of establishment, e.g., a coal mine, the appropriate Act should be obtained.)
 National Insurance (Industrial Injuries) Act 1946.
 Disabled Persons (Employment) Act 1944.
 Factory Orders 1948. (Ministry of Labour and National Service.)
 (All the above are published by His Majesty's Stationery Office.)
 "First-aid in Industry": British Medical Association, 1939.
 "Duties of and Ethical Rules for Industrial Medical Officers": British Medical Association, 1937.
 "Nursing Service to Industry and Commerce": The Royal College of Nursing, April 1948.

(2) *Special Publications*

- Reports no. 1 to 89 of the Industrial Health Research Board of the Medical Research Council, together with the Special Report Series, and the Pamphlet series.
 Welfare Pamphlet Series (Ministry of Labour).
 Annual Reports of the Chief Inspector of Factories (Ministry of Labour).
 Ministry of Labour Gazette (monthly publication).
 (All the above are published by His Majesty's Stationery Office.)
 Publications of the Royal Society for the Prevention of Accidents: "R.O.S.P.A.", 52 Grosvenor Gardens, London, S.W.1.

(3) *Books and Journals*

- Books**
 "Occupational Medicine and Industrial Hygiene", Rutherford T. Johnstone, A.B., M.D.: Henry Kimpton, 1948.
 "The Practice of Industrial Medicine", T. A. Lloyd Davies, M.D.: J. & A. Churchill, 1948.
 "Industrial Medicine". *The Practitioner Handbooks*. Edited by Sir Humphry Rolleston, Bt., G.C.V.O., K.C.B., M.D., F.R.C.P., and Alan Moncrieff, M.D., F.R.C.P.: Eyre and Spottiswoode (Publishers) Ltd., 1944.
 "Basic Principles of Ventilation and Heating", Thomas Bedford, D.Sc.: H. K. Lewis & Co., 1948.
 "Noxious Gases and the Principles of Respiration influencing their Action", Y. Henderson & H. W. Haggard: Reinhold Publishing Corporation, New York, 1943.
 "Occupational Diseases of the Skin", Louis Schwartz, M.D., and Louis Tulipan, M.D.: Henry Kimpton, 1939.
 "Eye Hazards in Industry", Louis Resnick: Chapman & Hall, 1941.
 "Industrial Toxicology", Donald Hunter, M.D., F.R.C.P.: Oxford University Press, 1942.

Journals:

- British Journal of Industrial Medicine*: British Medical Association (quarterly).
Occupational Medicine: American Medical Association (monthly).
Industrial Medicine: Industrial Medicine Publishing Company, Chicago (monthly).
The Journal of Industrial Hygiene and Toxicology: The Williams & Wilkins Company, Baltimore (ten issues yearly).

Finally, we recommend frequent visits to H.M. Stationery Office for all those engaged in industrial medical work. Apart from statutory health and safety regulations with which the medical officer must be familiar, there is a constant flow of publications from Government sources which contain most valuable and interesting information for those working in this field.

CURRENT THERAPEUTICS

XVII.—STREPTOMYCIN

By NORMAN B. CAPON, M.D., F.R.C.P.

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STREPTOMYCIN is an antibiotic substance produced by *Actinomyces griseus*, and was discovered by Schatz, Bugie and Waksman in 1944 during an extensive investigation of soil micro-organisms. Schatz and Waksman (1944) showed that streptomycin was active *in vitro* against certain gram-negative bacteria and the tubercle bacillus. Experimental animals suffering from tuberculosis and various diseases caused by gram-negative organisms were then treated (Jones, Metzger, Schatz and Waksman, 1944; Feldman and Hinshaw, 1944; Feldman, Hinshaw and Mann, 1945), and it was established that streptomycin was effective *in vivo* as well as *in vitro*. In 1946 the first large-scale clinical trial of streptomycin was reported from America (National Research Council, 1946).

MODE OF ACTION

Garrod (1948) studied the action of streptomycin on *Staphylococcus aureus* and showed that its action was bactericidal. The rapidity and extent of this action depended upon two main factors: the concentration of the drug and the number of organisms present. The most favourable circumstances were a small number of bacteria and a high concentration of streptomycin.

INDICATIONS

Streptomycin acts *in vitro* upon the following organisms:—

<i>Mycobacterium tuberculosis</i>	<i>Pseudomonas pyocyanea</i>
<i>Hæmophilus influenzae</i>	<i>Klebsiella pneumoniae</i> (Friedländer)
<i>Hæmophilus pertussis</i>	<i>Brucella abortus</i>
<i>Bacterium coli</i>	<i>Pasteurella pestis</i>
<i>Bacterium tularensis</i>	<i>Treponema pallidum</i>
<i>Salmonella typhi</i>	<i>Neisseria gonorrhoea</i>
<i>Shigella dysenteriae</i>	Streptococci
<i>Proteus vulgaris</i>	Staphylococci

In clinical trials, however, streptomycin has not proved effective against all these organisms, but it has a definite action in the following conditions (Medical Research Council, 1948a and b; Todd, 1949; Wilson, 1948a):—

(A) Tuberculosis

- (1) Tuberculous meningitis
- (2) Miliary tuberculosis
- (3) Tuberculous broncho-pneumonia in childhood
- (4) Pulmonary tuberculosis in adults
- (5) Tracheo-bronchial tuberculosis

(B) *Non-tuberculous conditions*

- (1) Meningitis due to *H. influenzae*, *Bact. coli*, *Ps. pyocyanea*, *Proteus* group and *Staph. pyogenes*.
- (2) Septicæmia due to *Bact. coli*, and *Ps. pyocyanea*.
- (3) Urinary infection due to *Bact. coli*, *Proteus* group, *Ps. pyocyanea*, *Strep. faecalis* and *Staph. pyogenes*.
- (4) Local sepsis due to *Bact. coli*, *Proteus* group, *Ps. pyocyanea*, *Staph. pyogenes* and *Strep. hæmolyticus*.

A number of patients with the following diseases have been treated with streptomycin but the results have been negative or indefinite:—

- (1) Infantile gastro-enteritis (Wilson, 1948a; Goettsch, *et al.*, 1948).
- (2) Typhoid fever (Wilson, 1948a; Capon and Todd, 1949).
- (3) Whooping-cough (Schwabacher, *et al.*, 1949).

Since February 1947, we have administered streptomycin to 76 patients in Alder Hey Children's Hospital, Liverpool, and the Royal Liverpool Children's Hospital, for the following conditions:—

Tuberculous meningitis	55 patients
Tuberculous broncho-pneumonia	6* "
Miliary tuberculosis	5 "
<i>H. influenzae</i> meningitis	6 "
Typhoid fever	2 "
Abdominal tuberculosis	1 "
Tuberculous pleural effusion	1 "
Total	76 "

* One patient who developed tuberculous meningitis during the course of tuberculous broncho-pneumonia is not included in these 6 patients, but is included in the 55 patients suffering with tuberculous meningitis.

ADMINISTRATION OF STREPTOMYCIN

Route.—The drug is given by intramuscular injection in the treatment of all the above conditions and in many cases the local concentration of the drug is augmented by direct application or injection. For example, in tuberculous meningitis the drug is introduced both intramuscularly and into the lumbar theca, cisterna magna, lateral ventricles, or into the interpeduncular space. In respiratory disorders it may be given by aerosol nebulization, and in intestinal tract infections the oral route has been used. Smith, Vollum and Cairns (1948) have shown that a varying degree of obstruction to the flow of cerebrospinal fluid occurs at the tentorial opening at some stage in almost all cases of tuberculous meningitis, and that this obstruction prevents the diffusion of streptomycin from the spinal theca to the lateral ventricles. This work suggests that the results of treatment would be more satisfactory if streptomycin were injected into the lateral ventricles at an early stage, and this should therefore be considered in every case of tuberculous meningitis.

Dosage.—Intramuscular dosage is based upon the weight of the patient, 0.02 g. of streptomycin per pound being given every twenty-four hours. This amount is given in divided doses every twelve hours, in a volume of

1 to 2 ml. of sterile distilled water. Intrathecally, a dosage of 0.05 to 0.1 g., in 5 to 10 ml. of sterile distilled water, is given once daily. Larger intrathecal doses are not recommended because they may cause toxic effects.

Rhythm and duration of treatment.—A survey of the published reports reveals that the regimens of treatment differ widely. In tuberculous meningitis, some workers give the drug for three to six months intramuscularly and intrathecally; others employ a continuous intramuscular course with short periods of intrathecal injections; whilst others use intermittent administration of both intramuscular and intrathecal injections. In the treatment of our 55 cases of tuberculous meningitis in children all these methods have been employed; but our experience to date suggests that the following basic regimen has proved to be the best:—

(1) Continuous intramuscular therapy for twelve weeks.

(2) Daily intrathecal injections for the first seven to ten days, followed by a rest period for seven to ten days, and then a further intrathecal course lasting for seven to ten days. Further intrathecal therapy may be required in some cases.

All workers agree that in tuberculous meningitis, intramuscular therapy alone is unsatisfactory: but we consider that a minimal number of intrathecal injections is desirable in children.

TOXIC EFFECTS

Local.—Pain at the site of injection may be severe, but it can be minimized by injecting the drug slowly and by the addition of 0.1 ml. of 2½ per cent. procaine to each streptomycin injection.

Histamine reaction.—Flushing, headache and a marked fall in blood pressure were reported shortly after streptomycin was introduced, but no such reactions occurred in our cases, and it is probable that impurities in the early samples of streptomycin were responsible.

Anaphylaxis.—Sensitivity to the drug may cause sudden collapse, with a weak, rapid pulse and bronchial spasm (Rosen, 1948). More commonly, sensitivity causes generalized skin rashes which may be morbilliform, scarlatiniform or urticarial in type; eosinophilia may also be observed, as in three of our cases. Manifestations of allergy were uncommon in our series and disappeared quickly when the drug was stopped for forty-eight hours. Gastric symptoms, such as nausea and vomiting, may occur, and anti-histamine drugs have relieved these symptoms (Bignall and Crofton, 1949).

Neurological.—Vestibular dysfunction causing dizziness, ataxia, loss of hearing and vertigo has been observed in patients with tuberculous meningitis treated with streptomycin, and in some cases it is difficult to decide if these symptoms are due to the disease itself or to the toxic effects of the drug. In one of our cases deafness was marked, and in another auditory acuity was diminished. Tremors of the head, arms and hands have been observed in eight of our patients receiving intrathecal streptomycin; in some this tremor was cerebellar in type and in others it was Parkinsonian.

Fatal toxic encephalopathy has also been attributed to streptomycin (Hunnicut, *et al.*, 1948). Intrathecal streptomycin may result in a marked pleocytosis in the cerebrospinal fluid, and in some of our cases figures of about 500 cells per c.mm. were frequent.

Renal.—Impaired renal function and nephritis may result from streptomycin therapy. In three of our cases casts and red blood cells were observed, and frank blood was passed by another patient. These abnormalities disappeared quickly when the drug was temporarily suspended, and no permanent renal damage would appear to have been sustained.

Painful erosive membranous *stomatitis* has been observed (Beham and Perr, 1948) in adults with pulmonary tuberculosis treated with streptomycin, and may be caused by the drug or may result from alteration of the oral bacterial flora (as with penicillin therapy). The condition cleared up within 14 days when the drug was discontinued, but reappeared when treatment was reinstituted.

Jaundice was encountered by Decourt *et al.* (1948) during the treatment of cases of tuberculous meningitis with streptomycin, but there is insufficient evidence to incriminate the drug. Other factors, such as the transmission of jaundice by syringes, or a ward epidemic of hepatitis (as in one of our patients), may be responsible.

Skin reactions affecting those who administer the drug have been observed (Strauss and Warring, 1947; Crofton and Foreman, 1948; Stringfellow, 1948; Rauchwerger, Erskine and Nalls, 1948). These reactions, which may appear after one month's exposure to the drug, consist in an initial erythema of the fingers, hands or elbows, followed by pruritus and a papulo-vesicular eruption. Photophobia, peri-orbital irritation and œdema may also be observed and are probably the result of auto-inoculation. Skin sensitivity tests (patch or intradermal) will confirm the diagnosis. Doctors and nurses using streptomycin are advised to wear rubber gloves and to take all reasonable precautions to avoid contamination with streptomycin powder or solution.

CLINICAL RESPONSE

(A) *Tuberculous conditions*

Before the advent of streptomycin, patients suffering from *tuberculous meningitis* usually survived for about four weeks. The most striking effect of the drug is to delay and sometimes arrest the disease process and so prolong life. In some patients whose abnormal clinical signs have disappeared and cerebrospinal fluid has become normal, the infection appears to be arrested. There are seven such patients in our series surviving ten to twenty-two months after beginning of treatment. It is unwise to claim such cases as cures, because experience shows that relapses and second attacks of tuberculous meningitis are not uncommon, and that the longer the period of observation after treatment the higher is the mortality rate. In our series, six patients have had recurrence of tuberculous meningitis and in one case this relapse occurred fourteen months after streptomycin

treatment was first given, and five months after apparent cure. Satisfactory response to a second course of streptomycin took place in only one of these six cases, although there was no evidence of increased resistance of the tubercle bacilli to the drug.

Tuberculous broncho-pneumonia in childhood shows a promising response to streptomycin. Of eight cases treated (Todd, 1949) five responded, two died and one showed temporary improvement.

Miliary tuberculosis may be confined to the lungs or may be part of a generalized dissemination involving the meninges. In our experience the former type of case responds more readily to streptomycin therapy; the general condition of the patient improves although the radiological appearances of the lung fields remain unchanged for several weeks. In our two patients who responded satisfactorily the miliary appearances were unchanged until the twelfth week of treatment, and then gradual improvement was seen over many weeks.

TABLE 1

Type of Case	Alive	Dead	Total
Tuberculous meningitis	10	29	39
Tuberculous meningitis and miliary tuberculosis	2	13	15
Miliary tuberculosis	2	3	5
Tuberculous meningitis and tuberculous broncho-pneumonia	—	1	1
Tuberculous broncho-pneumonia	5	1	6
Totals	19	47	66
Total tuberculous meningitis (all forms) ..	12	43	55

TABLE 2

Authors	Number of Patients	Minimum Period of Observation	Clinical "Cure"	Deaths
		months		
Medical Research Council, 1948a	105	7	27 (26 per cent.)	71 (67 per cent.)
Choremis, <i>et al.</i> , 1948	63	4	22 (34 per cent.)	34 (54 per cent.)
Rubie and Mohun, 1949*	54	8	16 (30 per cent.)	36 (67 per cent.)
Capon and Todd, 1949*	55	10	7 (12 per cent.)	43 (78 per cent.)

* Some cases in these series are included in the figures of the Medical Research Council, 1948a.

In two of our cases with miliary pulmonary tuberculosis and meningitis, however, radiological improvement was more rapid. In one case the miliary shadowing had disappeared by the twelfth week and in the other case by the tenth week. The latter patient came to autopsy two weeks after the

"negative" X-ray, and miliary tubercles were seen macroscopically; and on microscopical examination the miliary tubercles showed evidence of healing. The details of the results of our cases are shown in table 1. Table 2 shows the results of treatment of tuberculous meningitis in other centres.

(B) *H. influenzae meningitis*

Both in this country and in America results have shown that streptomycin is probably the most effective therapeutic agent at present known for influenza meningitis, and that failures are almost entirely due to the rapid development of resistance to streptomycin (Wilson, 1948b). We consider that it is advisable to administer sulphonamides in addition to streptomycin. In exceptional cases (Cathie and Weller, 1948) the addition of rabbit antiserum may also be required.

Of eleven cases reported by Smythe (1948), eight responded satisfactorily to streptomycin, and in one of the patients who died the organism was shown to have become resistant. Roscoe and Gleeson-White (1948) reported four cases; three of these showed a rapid response with complete recovery, whilst in the fourth case the organism became resistant to streptomycin.

We have treated six patients, aged five months to three and a half years, with streptomycin; in all cases the response was rapid and five recovered fully. Streptomycin was given intramuscularly in a dosage of 0.02 g. per pound per twenty-four hours for from nine to fourteen days, and daily intrathecal injections of 0.05 to 0.1 g. were given for seven to twelve days. Penicillin and sulphonamides had been given to these patients previously, but without therapeutic effect. One of our patients was discharged from hospital with no abnormal signs and a normal cerebrospinal fluid, but was re-admitted four weeks later with pneumococcal meningitis which rapidly proved fatal.

DRUG RESISTANCE

In diseases caused by *Bact. coli*, *H. influenzae* and *M. tuberculosis*, particularly in the adult pulmonary type, the development of resistance to streptomycin has been reported. The time at which this resistance emerges varies with the organism. Fleming (1948) considers that with *Bact. coli*, resistance may develop within forty-eight hours of the administration of streptomycin. In adult pulmonary tuberculosis, resistance usually develops in the second month of treatment (Medical Research Council, 1948b). A further study of some of these cases (Crofton and Mitchison, 1948) showed that in 12 cases resistant strains were isolated from the forty-second day of treatment and the rise in resistance varied from 4 to over 4000 times that of the control strain H37Rv. Resistant strains of tubercle bacilli were isolated in three of our cases of meningitis on the forty-seventh, seventy-sixth and one-hundred-and-seventy-sixth day after streptomycin therapy was started.

Two theories to account for this phenomenon of bacterial resistance have been suggested. Either the tubercle bacilli may acquire resistance, or the organisms vary in their sensitivity to streptomycin, the more resistant organisms continuing to multiply while the sensitive ones are destroyed.

The latter view is supported by the work of Pyle (1947) in which tubercle bacilli obtained from the sputa of eight patients with pulmonary tuberculosis were grown on Herold's egg medium containing varying concentrations of streptomycin. Even before streptomycin had been administered to these patients, tubercle bacilli from

the sputum of seven of them were found to include resistant strains. After four to six weeks an increase in the number of these resistant strains was observed.

Massive dosage of streptomycin at the beginning of treatment, intermittent streptomycin therapy, and the use of other drugs in combination with streptomycin, may all help to combat this problem of drug resistance.

COMBINATION OF DRUGS

Para-amino-salicylic acid, sulphathione and promizole have been used singly or in association with streptomycin in the treatment of some tuberculous conditions. Para-amino-salicylic acid (Lehmann, 1946; Dempsey and Logg, 1947) has been given to patients with pulmonary tuberculosis, tuberculous enteritis, renal tuberculosis and tuberculous meningitis. Sulphathione (Madigan *et al.*, 1947) has been used for fibrocaceous pulmonary tuberculosis, miliary tuberculosis, renal tuberculosis and tuberculous disease of the spine. Promizole (Lincoln *et al.*, 1948) has been given to children suffering from tuberculous meningitis. The results of treatment with these drugs have been inconclusive, although there is evidence of the synergism of sulphathione and streptomycin *in vitro*.

FACTORS AFFECTING RESPONSE TO STREPTOMYCIN

Stage of disease.—Early cases of *tuberculous meningitis* with a short history and relatively few abnormal signs are the most likely to benefit. Consideration of the following features should ensure earlier diagnosis:—

(1) *History of contact* with a known case of active pulmonary tuberculosis is important, for in selected groups of children suffering from primary tuberculosis, Wallgren (1934, 1941) has shown that tuberculous meningitis develops within three months of the primary infection in over 80 per cent. of cases. In 26 of our 55 cases a positive contact history was obtained, in 12 cases radiological examination of other members of the family was negative, and in 17 cases the relatives refused X-ray examination.

(2) *Change of temperament* is an early feature: "The child not only limits his physical and mental activities but, over and above that, withdraws from contact with others and retires within himself" (Craig, 1948).

(3) The importance of recognizing minimal degrees of *neck resistance* cannot be overstressed, and even a suspicion of this finding should suggest the need for further investigation, including examination of the cerebrospinal fluid and thorough examination of the fundi for choroidal tubercles.

(4) *The Mantoux reaction*, especially in the younger child, is invaluable. A positive test in a child with even minimal signs in the central nervous system warrants immediate admission to hospital for further investigation. In 32 of our 55 cases the Mantoux test was positive in a dilution of 1 in 10,000, and in 26 cases in a dilution of 1 in 1000. In 7 cases the Mantoux reaction was negative, even to a strength of 1 in 100 in six cases.

(5) *Examination of the cerebrospinal fluid* may confirm the diagnosis, but in a very early case, unless tubercle bacilli are seen in direct examination of a film, it is not necessarily diagnostic. The fluid is translucent, usually contains an excess of lymphocytes, and has a raised protein content. A low or falling level of sugar is, perhaps, the most useful single finding. The chloride level is usually normal in the early case. In 52 of our cases tubercle bacilli were isolated from the cerebrospinal fluid; 45 were seen in direct films and the remainder proved positive on culture.

Isolation of the tubercle bacillus from sputum, gastric lavage or cerebrospinal

fluid, either by direct examination, by culture, or by guinea-pig inoculation, should be attempted in every suspected case.

(6) *The age of the patient* has a definite bearing on the outcome of the disease, and the results of the Medical Research Council trials (1948a) indicate that the prognosis is particularly poor for patients under the age of three years (see table 3).

TABLE 3

Age	Treatment	Number of Cases	Condition after 120 Days	
			Good	Dead
Under three years ..	Combined intra-muscular and intra-theal	24	4 (17 per cent.)	18 (75 per cent.)
	Intramuscular only	9	0	9 (100 per cent.)
Three years and over ..	Combined intra-muscular and intra-theal	48	21 (44 per cent.)	24 (50 per cent.)
	Intramuscular only	19	3 (16 per cent.)	13 (68 per cent.)

(7) *Type of tuberculous meningitis.* The use of streptomycin has prolonged life in many patients suffering with tuberculous meningitis and this has enabled morbid anatomists to study the changes due to an infection which has operated over much longer periods than formerly. Furthermore, fresh interest has been aroused regarding the possible modes of spread of tuberculosis to the meninges, and the type and severity of the tissue-reaction which may be evoked. Evidence is accumulating that even during the primary stage of tuberculous infection there is often a blood-borne dissemination of organisms; but local "disease", as revealed by clinical signs, does not invariably develop because the patient's natural resistance may be sufficient to overcome the scattered pockets of invaders. This is the probable explanation of cases of so-called "serous tuberculous meningitis" (Lincoln, 1947; Choremis and Vrachnos, 1948; Mann, 1948; Rubie and Mohun, 1949) in which children who have an established intrathoracic tuberculous lesion, slight neck stiffness, an increase of cells and occasionally tubercle bacilli in the cerebrospinal fluid, recover spontaneously within seven to ten days. We have observed three such cases of primary pulmonary tuberculosis with transient meningeal reaction, and in one case undoubted tuberculous meningitis developed six weeks after this meningeal episode.

Is it not probable that a mild degree of tuberculous infection of the meninges occurs more frequently than clinical records would suggest, and that at present the diagnosis of "tuberculous meningitis" is made only in those patients who have an overwhelming meningeal infection against which their resistance is almost powerless? If this hypothesis is supported by the results of further investigation it is likely to have a most important bearing upon the indications for streptomycin treatment. It is the relatively small, early and superficial lesion which reacts best to streptomycin; and to put the drug to its most effective use it may be necessary to employ it at a stage before the onset of those symptoms and signs which are at present accepted as the clinical criteria for the diagnosis of meningitis. This may eventually imply that the cerebrospinal fluid should be examined for tubercle bacilli and for any cytological or chemical abnormality at regular intervals in children suffering from a primary tuberculous infection.

Our observations have led us to the general impression that tuberculous meningitis consequent upon a recent blood-borne infection makes a some-

what better response to streptomycin than an infection spreading to the meninges from a cerebral or cerebellar tuberculoma (Rich focus). Although sealed off temporarily as a result of streptomycin therapy, such a tuberculoma—particularly if situated near the surface of the brain—may subsequently break down and release tubercle bacilli into the subarachnoid space, giving rise to a further attack of tuberculous meningitis.

We wish to thank our colleagues at Alder Hey Children's Hospital, Liverpool, and at the Royal Liverpool Children's Hospital, for their wholehearted cooperation.

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REVISION CORNER

PRESENT TRENDS IN PROTECTION AGAINST CHILDHOOD INFECTIONS

THE past three years have provided a stimulus to the profession in their efforts to control one of the most serious infectious diseases in childhood, namely diphtheria. Diphtheria immunization alone can account for the remarkable reduction both in incidence and mortality from this disease. It is now apparent that by a continued effort to ensure that each child is fully protected, diphtheria in the near future will cease to be a major problem. It is therefore an opportune moment to consider the maintenance of these satisfactory results and to note contemporary knowledge concerning the control of whooping-cough and measles.

DIPHTHERIA

Maintenance of immunity.—The level of immunity in an individual is a factor liable to variation and children will differ in their response to the injection of immunizing antigen. For example, one child may remain permanently Schick negative and presumably protected against diphtheria following primary immunization in infancy, whereas another child will relapse and become once more susceptible to infection at a varying interval after primary immunization. It is necessary to have concise ideas as to the best method to maintain a satisfactory level of immunity for the average child. To this end, primary active immunization should be carried out at about nine months, so that the two injections are given before the first birthday. Subsequently, the level of immunity will be maintained by giving a single reinforcing or booster injection at the age of five years and a similar single booster injection at ten years. Such a plan will ensure that almost every child is maintained at a satisfactory level of protection.

Present methods of immunization.—Alum-precipitated toxoid (A.P.T.) is the most popular antigen and has proved to be satisfactory. It has, however, two disadvantages:—(1) Batches of the material may vary in antigenic or immunizing potency. This is due to the aluminium hydroxide content which does not form

TABLE I
METHOD OF DIPHTHERIA IMMUNIZATION

Age	Preparation	Number of injections and dosage	Interval between injections
9 months to 7 years	A.P.T.	2 injections each of 0.5 ml.	4 weeks
7 to 14 years	A.P.T.	2 injections: 1st, 0.2 ml. 2nd, 0.5 ml.	4 weeks
14 upwards + reactors ..	T.A.F.	3 injections each of 1 ml.	3 weeks
All ages from 9 months upwards	P.T.A.P. P.A.P.T.	2 injections each of 0.5 ml.	4 weeks

an entirely stable suspension with diphtheria toxoid. (2) Unpleasant local and general reactions may occur, especially in those over ten years and when booster injections are given. In order to overcome both of these disadvantages two preparations are now under trial and have been favourably reported upon. In both, aluminium phosphate is used in place of aluminium hydroxide. They are known as

purified toxoid alum-precipitated (P.T.A.P.) made by Holt, of St. Mary's Hospital, and phosphate-absorbed purified toxoid (P.A.P.T.) made by Burroughs Wellcome.

Opinion with regard to dosage has become modified. For primary immunization in infancy and up to seven years any of the alum-precipitated toxoids should be given by two equal injections of 0.5 ml. Formerly the first dose was smaller—0.2 ml. In primary immunization of children over seven years and up to fourteen years there is more liability to reaction, therefore if A.P.T. is used the first injection should be 0.2 ml. followed by 0.5 ml. Children over fourteen years and adults immunized for the first time are best treated with toxoid antitoxin floccules (T.A.F.), with the usual three doses of 1 ml. at intervals of three weeks. Reaction occurs more often with booster injections and therefore a single dose of 0.5 ml. A.P.T. is given up to seven years, and to older children a single dose of 1 ml. T.A.F. The newer preparations, P.T.A.P. and P.A.P.T., may displace the older prophylactics and if they do so will provide a standard dosage of 0.5 ml. for the two primary immunizing injections at all ages and a similar dose for subsequent reinforcement or booster treatment. These points are summarized in table 1.

For the immediate control of diphtheria in the presence of known infection passive immunization with 500 units of diphtheria antitoxin together with concurrent active immunization is the best practice.

WHOOPING-COUGH

Present position regarding active immunization.—Controversy persists as to whether or not any vaccines so far used afford a good measure of protection against whooping-cough. No doubt exists as to the need for an efficient antigen. In 1946, whooping-cough for the first time surpassed the diphtheria mortality in England and Wales, causing 808 deaths against 455 for diphtheria. The optimum age for immunization is early infancy, preferably at three months, because the disease is most severe and fatal in the first year of life.

Methods of immunization.—No satisfactory method other than clinical trial is as yet available to standardize the antigenic potency of whooping-cough vaccines. Dosage must be related to the concentration of the vaccines. They usually contain either 10,000 or 20,000 million organisms per ml. The English vaccines are roughly

TABLE 2
METHOD OF WHOOPING-COUGH IMMUNIZATION

<i>Strength of vaccine</i>	<i>Number of injections</i>	<i>Dosage of vaccine in injection</i>	<i>Total dosage in millions of organisms</i>	<i>Time intervals between injections</i>
20,000 million organisms per ml. 	3	1st and 2nd, 0.5 ml. 3rd, 1 ml.	40,000	1 month
10,000 million organisms per ml. 	3	1 ml. for each	30,000	1 month

three times the concentration of American products. Three injections are given at monthly intervals, the site of injection often being varied. The first one is given into the arm and the second and third into each thigh.

General reaction with pyrexia (101° to 103°F. [38.3° to 39.4°C.]) malaise and irritability, is not uncommon, appearing soon after treatment and subsiding within forty-eight hours. Occasionally, spasmodic cough develops which clears up within a week. It is not known whether this cough is to be regarded as a complication or is an occasional fortuitous event. The present views concerning dosage of vaccines are summarized in table 2.

COMBINED DIPHTHERIA AND WHOOPING-COUGH IMMUNIZATION

Both diphtheria and whooping-cough antigens may be given together, and preparations are available containing a mixture of the two antigens which are given in the same injection. The antibody response is not adversely affected but it must be ensured that an adequate dosage of both prophylactics is given. The variation in optimum age of choice for immunization in these two diseases will restrict the usefulness of this method. As has been mentioned, whooping-cough immunization should be begun earlier than diphtheria immunization

MEASLES

Little recent progress has been made to provide means for the prevention of measles. No method of active immunization is available, and passive immunization to prevent or attenuate imminent infection has to be relied upon.

Methods of immunization.—The serum of a patient convalescent after measles contains antiviral material and so does the serum of an adult who has had measles in childhood. The adult serum contains antiviral properties in a less concentrated form. The gamma globulin fraction of adult serum and also globulin extracts from the human placenta contain this factor in a concentrated form. It is from these sources that prophylactic substances are obtained for the temporary prevention or the attenuation of an incipient measles infection. For prevention, the antiviral product must be given within the first five days of exposure to infection. Subsequently, administration up to the ninth day will often attenuate an attack. By giving half the dose of antiviral substance during the first five days after exposure, the attack may also be attenuated. The use of these products is shown in table 3.

TABLE 3
METHOD OF ADMINISTRATION OF ANTI-MEASLES PRODUCTS

Product	Minimum dose for 3 years and under	Dosage over 3 years	Object desired	
			Protection	Attenuation
Convalescent serum. . . .	5 ml.	10 ml.	1st to 5th day	6th to 9th day
Adult serum	10 ml.	20 ml.	1st to 5th day	ditto
Placental extract	2 ml.	4 ml.	1st to 5th day	ditto
Gamma globulin	2 ml.	2 ml.	1st to 5th day	ditto

Both convalescent and adult serum have given rise to cases of homologous serum jaundice, and although this is of rare occurrence it has restricted their use. Placental extract is liable to give severe local and general reactions but they require no special treatment and usually subside within forty-eight hours. The product of choice is therefore gamma globulin, but supplies of this are not yet readily available in this country.

W. POWELL PHILLIPS, O.B.E., M.R.C.S., L.R.C.P., D.P.H.

THE CARE OF THE NAILS

THE nails are formed as a modification of the normal process of keratinization of the skin and, like the skin, they are affected by both external traumatic influences and by internal disturbances. In addition, in view of the construction of the nail with the overlying nail fold, it is commonly affected by some infective process which gains access to the depths of the fold.

The healthy nail is gently convex in both the transverse and longitudinal axes, having a smooth shiny surface, a strong regular free edge, and transmitting evenly the colour of the underlying nail bed. The size of the lunula varies greatly in different individuals and races. The rate of growth is influenced by the state of health of the individual and slightly by the seasons, being more rapid in summer than in winter. On the average, the finger nail grows 1 mm. per week; the rate of growth of the toe nails is about one-quarter of this.

The only care required for healthy nails is regular paring, and with the finger nails the resulting length and shape is largely determined by the amount of manual work the individual does and his, or her, own particular taste. The method used for paring the nails is again a matter for the individual's choice, since it is *not* possible for the nail growth, which starts below the nail fold, to be materially influenced by the way the free edge is pared. In the case of the toe nails, the common practice is for the free edge to be cut straight, allowing the corners to ride over the skin of the toes with the idea of preventing "in-growing" of the nail. Actually, the method of cutting the nail has probably little bearing on the development of an in-grown toe nail; the factors mainly responsible for this are tight-fitting shoes or too small socks which force the body of the toe into the nail. In order to make the finger nails look tidy, the cuticle is usually pressed down off the nail into the nail fold, but this must be done with gentleness and care, since the cuticle serves as a seal to the nail fold, and damage to this by violent manicure or over-use of "cuticle remover", allows infection to enter the nail fold.

Of diseases affecting the nail, I shall mention only those which can easily be prevented or cured by reasonable care. Congenital abnormalities, deformities and dermatoses involving the nail will not be discussed.

EXTERNAL INFLUENCES AFFECTING THE NAILS

It is not common for *irritants* encountered at work or in the home to damage the nails directly, since any such substance which would damage the nail affects the surrounding skin much earlier and so is avoided. The greatest group of irritants damaging the nails are *cosmetics*. After prolonged use of nail varnish, the nails become brittle and tend to flake off at the free edge—it is probable that varnish remover is the chief offender. This condition is cured either by stopping the use of the cosmetics or by using an emollient cream occasionally to replace the natural fats and moisture removed by these substances. R. G. Harry ("Modern Cosmetology", London, 1944, p. 304) gives the following formula for a nail cream which should be applied on going to bed, several times a week:—

Lanoline	15 per cent.
Cocoa butter	8 per cent.
Beeswax	12 per cent.
Liquid paraffin	30 per cent.
Cetyl alcohol	3 per cent.
Water	30 per cent.
Borax	1 per cent.
Cholesterol	1 per cent.

Trauma of the cuticle is largely responsible for infection in the nail fold. This condition is much more common in women than in men, as is to be expected, since the two most common predisposing causes are manicure damage and frequent wetting of the fingers, particularly in the alkaline solutions of household cleansing agents. The patient complains of tenderness and throbbing of the nail folds of one or more fingers and on examination, there is, characteristically, redness and swelling of the skin just proximal to the nail fold, producing the so-called "bolster". In every case the cuticle of the affected nail is missing, and it is possible to pass a

fine probe down between the nail and the overlying skin for distances up to $\frac{1}{2}$ cm. Occasionally, a bead of pus can be expressed from this area. The infecting organisms vary: the most common is the staphylococcus; monilia may be isolated but this is perhaps a secondary invader. If left untreated, this condition may persist for years and the nails of the affected fingers are ridged and, with more severe infection, they may be shed. Treatment consists in keeping the affected fingers dry—not an easy thing for a housewife—and I have found twice daily applications of Castellani's paint most useful. In obstinate cases, a series of three X-ray exposures (133r 85 k.v. 5 ma. 0.5 mm. Al), at fortnightly intervals, is beneficial.

The factors predisposing to *fungus infection* of the nails are not known—the majority of the patients I have seen are women, and most have, or have had previously, active dermatophytosis of the feet. In involvement of the finger nails, the infection usually starts at the side of the nail. This becomes a dirty grey colour; there is a good deal of heaping of debris between the nail and the nail bed, and the affected part of the nail crumbles away. The process slowly progresses to involve the whole nail and, although one or more fingers may be affected, it is unusual for the condition to attack all the nails. The diagnosis is established by isolating the causative fungus which is found most easily on the under surface of the nail; scrapings from this region are macerated in 20 per cent. liquor potassæ, and the highly refractive mycelial elements of the fungus are seen microscopically. Psoriasis of the nails must be considered in the differential diagnosis. Treatment of onychophytosis is tedious and difficult. If the toe nails are involved, any treatment short of total extirpation of the nails is probably useless, as the condition will always recur. In the finger nails, it is sometimes possible to cure the condition by less radical measures. Daily removal of affected nail tissue by filing or scraping with broken glass and then applying some fungicide is worth trying. Castellani's paint is useful because it can reach easily the affected areas. Again, superficial X-ray therapy helps some of these cases, possibly by controlling secondary inflammatory reaction. If such measures do not cure the infection, it is necessary to remove the whole nail under local anæsthesia, and to prevent reinfection of the new nail, the nail bed should be dressed daily with 1 per cent. gentian violet solution for fourteen days following removal. In the most resistant cases, the nails have been extirpated and nail beds destroyed to prevent regrowth, but fortunately such cases are uncommon.

SYSTEMIC DISTURBANCES AFFECTING THE NAILS

The state of the general health is often reflected in the nails. Examples of specific nail involvement are seen in clubbing of the fingers and in the flattened or spoon-shaped nails associated with hypochromic achlorhydric anæmias. A severe illness will often leave its trace as a transverse line on the nail, indicating some diminution of nail formation during the time of the illness. These lines—Beau's lines—gradually grow out with growth of the nail.

The nails are sometimes affected in circulatory impairment of the hands or feet, but there is no evidence that calcium deficiency plays any part in nail disturbances. I have had one case in which small doses of thyroid seemed to cure splitting of the nails arising for no obvious cause. It has been stated that vitamin A increases nail growth and that vitamins B and D clear up certain cases of ridged and furrowed nails. In dealing with conditions of the nails in which all are involved, some underlying systemic disease must be sought, and treated. The dermatological maxim that the skin, with its appendages, is a living organ and, as such, is an integral part of the body, must always be borne in mind in the care of the nails.

H. R. VICKERS, V.R.D., M.B., M.Sc., M.R.C.P.

NOTES AND QUERIES

Discharging Sinus in Right Iliac Fossa

QUERY.—A woman patient, married, aged fifty-four, came to see me about a month ago, complaining of a discharging sinus in the right iliac fossa. She gave the following history:—About Christmas she noticed a soreness in the lower part of her abdomen, made worse by movement. A few days later there was a red area, "like a burn", where the pain had been. Kaolin poultices were applied, and the red area came to a head, and finally burst, discharging some "bloody matter". The redness subsided and a small hole remained, which has discharged a thin milky fluid ever since. The patient has had two uneventful pregnancies and no serious illnesses. She has not had any indigestion and has not lost weight. Her bowels have been regular and she has no trouble with micturition. Her periods ceased five years ago. She had no pain before the soreness appeared in her abdominal wall, and this soreness was very slight and quite superficial. Her main complaint is of the soiling of her clothes, and of the need to wear a square of lint over the opening. She looks healthy. The opening is a small puckered sinus, that will just admit a probe, about one inch below McBurney's point. The discharge is opalescent. On microscopic examination a few pus cells and cocci can be seen, but no actinomycotic granules have been seen or found by the pathologist. Her temperature and pulse are normal, and hæmatological investigation reveals no abnormality beyond a slightly raised blood sedimentation rate. A barium meal and barium enema show no demonstrable lesion in the right iliac fossa or anywhere in the alimentary tract. The appendix is not shown, but there is no tenderness at the ileocaecal angle. I should be grateful for your help in the elucidation of this difficult case.

REPLY.—The history in this case seems almost certainly to exclude cancer, acute appendicitis, or tuberculosis (except that a calcareous ileocaecal gland quiescent since childhood may have undergone secondary infection with pyogenic organisms). Any infection that makes its way to the surface leaves a discharging hole for a time, but if a sinus persists the reason is usually one of four: there is a foreign body at the bottom of it; it is infected with a persistent organism (tubercle, syphilis or actinomycosis); its walls are too rigid to collapse; or it communicates with a cavity and is therefore a fistula rather than a sinus. In young women a fifth reason must be considered: that the sinus is self-inflicted and self-maintained. The cure of

a sinus (except in the last instance) is surgical, but before an operation is undertaken it is even more important to know the length, direction, and termination of the track than to know its cause. The most common explanation for a sinus appearing spontaneously on the abdominal wall of a healthy middle-aged woman is diverticulitis; it is not the most likely one in this case because the discharge has apparently never been faecal, and because diverticula are rare, although not unknown on the right side. Actinomycosis of the appendix or cæcum is more probable, and is not excluded by several failures to find the organism. Neither a single diverticulum nor an actinomycotic infection would necessarily be shown by a barium meal or enema. The most helpful investigation will be an X-ray of the track, rendered visible by the injection of a radio-opaque substance. Lipiodol and its various substitutes are unsatisfactory for this purpose, for an oily medium injected down a moist track tends to become a series of globules in the finer branches, and not to enter the ultimate ones at all. Pyelosil, diodrast, or one of the many water-soluble contrast media used for pyelography and angiography, should be used. I have recently seen a residual stone in the common bile duct missed in a lipiodol X-ray and shown up subsequently when pyelosil was used. In this case the source of the discharge, whether an actinomycotic appendix, a single diverticulum or a calcareous gland, is probably small and local, and amenable to radical surgery when it has been demonstrated in this way.

HENEAGE OGILVIE, K.B.E., D.M., M.CH., F.R.C.S.

Malaria Prophylaxis in Children

QUERY.—I intend to take my infant son, at the age of four to five months, to West Africa where it is customary to take an antimalarial drug daily as a prophylactic. I should be grateful for your advice on which is the safest drug, and the appropriate dose for a child of this age.

REPLY.—The compound of choice for suppression of malaria in children is paludrine. The dose recommended for children from birth to the age of six years is 25 mg. daily or every other day, continued for a month after leaving the endemic area. Tablets of paludrine supplied commercially are standardized to contain 100 mg.; the dose for children is thus one-quarter of the standard tablet. The child should be encouraged to drink freely when given the drug. The dosage recommended above has been tried for some time now with success in the British

African Colonies. No toxic effects have been recorded. Therapeutic dosage with paludine in children should be supervised by a doctor. When I was in Africa last year I saw a very young child with brown discoloration of the distal phalanges of the fingers. This was said to be due to paludrine, but I found no real evidence connecting it with the drug, and in fact saw such discoloration in children who were not receiving it.

PROFESSOR B. G. MAEGRAITH, M.B., D.PHIL.

Urine During Arsenical Treatment

QUERY.—Before the injection of arsphenamine we have been adding four drops of a 3 per cent. solution of paradimethylaminobenzaldehyde and four drops of 50 per cent. hydrochloric acid to 10 ml. of urine. I should be grateful for answers to the following points:—(a) What is the significance of the appearance of pink or orange colours in the urine (as opposed to the deep red colour indicating pathological amounts of urobilinogen)? (b) What is the effect on treatment of the appearance of these colours?

REPLY.—The red colour produced in urine under the conditions described might be due to urobilinogen, indole, or rarely to porphobilinogen. The addition of a saturated sodium acetate solution after the hydrochloric acid is recommended, as it intensifies the colour from urobilinogen and porphobilinogen and reduces it due to indole. Any effect produced by arsenical treatment would probably be due to alterations in liver function and would affect mainly the urobilinogen excretion.

PROFESSOR N. F. MACLAGAN, M.D., D.Sc.

Radiology in Intestinal Tuberculosis

QUERY (from Malaya).—Could you let me know particulars of the Brown-Sampson roentgen ray technique for the diagnosis of intestinal tuberculosis? The textbooks on X-ray diagnosis do not mention this, but I found it referred to in John Alexander's "Collapse Therapy in Pulmonary Tuberculosis".

REPLY.—The original paper by Brown and Sampson on the technique for the early X-ray diagnosis of ulcerative tuberculous colitis appeared in the *American Journal of Roentgenology*, 1919, 6, 625. This consisted of examination of the colon by opaque meal and opaque emulsion. The authors published a book on intestinal tuberculosis in 1930 ("Intestinal Tuberculosis", 2nd edition, London, 1930) in which the findings in this condition after radiological examination are summarized. They state that as a rule in those cases which give

positive X-ray findings the general motility of the bowel, especially the caecum and ascending colon, is greatly increased. Characteristic spastic filling defects are interpreted as indicating the presence of ulceration and persistent segmentation, and later dilatation may show in this condition in the ileum.

For the full findings the reader is referred to the original writings, but it should be pointed out that since these were published the technique of examination by radiological methods has advanced so much, especially in the examination of the small intestine, that reference should be made to the more recent techniques in examination.

JOHN McLAREN, M.R.C.S., D.M.R.E.

Disinfection of Doctor's Waiting-Rooms

QUERY.—Could you give me some information on the best method of disinfection of my waiting-room? I was considering some type of ultra-violet apparatus and possibly, in addition, a spray combining an antiseptic. Would you let me know your views on the merits of these measures?

REPLY (from a bacteriologist).—Nearly all authorities are agreed to-day that the best way of dealing with aerial disinfection in a room is by adequate ventilation. This could be arranged fairly simply for the waiting-room by using a fan and some type of filter. The chief problem involved is that of warming incoming filtered air. It is generally accepted that the bacterial pollution of the air can be reduced by the use of ultra-violet light, provided the dust content of the air is small and the humidity is low.

Hay Fever Following Childbirth

WITH reference to the note on the above subject (*The Practitioner*, February 1949, 162, 165) a reader writes:—"I should like your correspondent to consider the following suggestions: (1) His wife has probably developed a hypochlorhydria during pregnancy, and almost certainly she has it still. She should take 10 or 15 drops of dilute hydrochloric acid, suitably prescribed in syrup and flavoured, in water before meals three times daily. (2) She will not recover until she is restored to her full vitality. This will not occur while she is feeding the infant, which should be weaned. I make it a rule to discourage breast feeding in asthmatic patients. (3) A spray such as riddobron is worth trying. (4) Elaborate care should be taken to see that any probable irritant, such as feather pillows, eiderdown coverlets, and fresh flowers, should be removed, especially from the bedroom.

PRACTICAL NOTES

The Eyes in Mongolism

THE findings in the eyes in 67 mongols are recorded by R. F. Lowe (*British Journal of Ophthalmology*, March 1949, 33, 131). Lens opacities of three types were commonly found: arcuate opacities, sutural opacities and flake opacities. Refractive errors were measured in 35 cases, and one-third were found to have high myopia. Nystagmus was present in nine cases, whilst 22 had constant strabismus, which was always convergent and horizontal. Eight had bilateral squint due to high myopia. The iris often showed thinning of the stroma peripherally with a speckled appearance. This is attributed to generalized vascular hypoplasia. The visual acuity was often poor, due to myopia, nystagmus, strabismus, and lens opacities, and it is recommended that a full ophthalmological examination should be made of any mongol who is to receive special schooling. Extra-ocular inflammations, which used to be common in mongols, are now seen less often since the introduction of the sulphonamides and penicillin, but nine cases of trachoma were found in this series. Intra-ocular inflammation is no more common in mongols than in the general population, and only two cases were found. No characteristic changes were found in the fundus oculi.

Vitamin E for the Menopausal Syndrome

ACCORDING to R. S. Finklater (*Journal of Clinical Endocrinology*, January 1949, 9, 89), "vitamin E is a valuable aid in the treatment of menopausal patients in whom oestrogens are contra-indicated". The conditions which are said to contraindicate the use of oestrogens include a familial or personal history of malignant disease; the presence of precancerous conditions such as uterine fibroids, cervical polypi, chronic mastitis; women in whom the menopause is accompanied by metromenorrhagia; and women in whom the administration of follicular hormone produces vaginal bleeding. The results are given of the use of vitamin E in 59 such menopausal women and another seven in whom there was no contraindication to the use of oestrogens. The daily dose of vitamin E ranged from 20 to 100 mg. (average, 30 mg.) in divided doses, and treatment was continued for ten days to seven months (average, 31 days). Good to excellent results were obtained in 31 patients (47 per cent.), fair relief was obtained in 16 (24.2 per cent.), whilst no benefit was noted in 19 (28.8 per cent.). In 17 patients who had obtained good results from vitamin E, the substitution of a placebo was followed by a recur-

rence of symptoms which disappeared again when the administration of vitamin E was re-instituted. No changes in the breasts, uterus or vaginal epithelium were observed following vitamin administration, and it is stated that there is no contraindication to its use. On the other hand, it is pointed out that oestrogens give "more rapid and complete relief than vitamin E in most cases".

Treatment of Parkinsonism

THE following mixture is recommended for daily use by a sufferer from Parkinsonism (*Lancet*, February 26, 1949, i, 364):—

Tincture of stramonium	8 ml.
Tincture of belladonna	0.5 ml.
Pilocarpine nitrate	1 mg.
Hyoscine hydrobromide	0.8 mg.
Water	to 15 ml.

The mixture is stated to eliminate the symptoms of tremor and difficulties in movement and writing—in fact, the patient "may feel for a time just like an ordinary person". The mixture, which produces considerable dryness of the mouth, should be taken (10 ml.) just after breakfast. Strong coffee should be avoided, as in conjunction with the mixture it may cause indigestion. The second dose (5 ml.) is taken in the early afternoon, and the third (5 ml.) in the evening, only if it is desirable to avoid tremor, which may reappear about 8 or 9 p.m. The muscular relaxation produced by the mixture may at first cause considerable lassitude, and temporary increased tendency to fall forward; these become less in a few days. There may be some effect on accommodation when accurate vision is required, in which event a lens or additional spectacles may be necessary. Finally, it is essential to keep an adequate supply of the mixture at hand, as when the patient becomes fully accustomed to it, neglect to take the usual maximum dose at breakfast time may result in nausea and sweating. The optimum dose and number of doses in relation to meals should be ascertained by trial at the beginning of treatment, and the feelings of malaise, lassitude and muscular limpness, which soon wear off, should be disregarded, as the "ultimate effect is to make walking very much easier, and enjoyable".

Fifty patients with Parkinson's disease have been treated with "parpanit" by R. S. Schwab and D. Leigh (*Journal of the American Medical Association*, March 5, 1949, 139, 629). The drug was given in initial dosage of 12.5 mg. five times daily in conjunction with previous medication; the dosage was slowly increased with decrease in the other medication, until on the fourth or fifth day the patient was receiving

parpanit alone, dosage being slowly increased until the mildest toxicity was experienced, and then reduced to a level causing minimal or no side-effects, and so maintained for several weeks or months. Results indicated that parpanit therapy was superior to other medication in 65 per cent. of the cases; the degree of improvement, chiefly diminution in rigidity, was about 25 per cent. Emphasis is laid on the fact that the drug must be administered cautiously in divided doses, five times daily, careful watch being kept for side-effects from overdosage (see also *The Practitioner*, August 1948, 161, 146).

Dosages for Children

SOME interesting features of current practice at the Adelaide Children's Hospital, South Australia, are discussed by S. A. Downie, the chief pharmacist to the hospital (*Pharmaceutical Journal*, January 15, 1949, 162, 44). Sulphadiazine is the most widely used sulphonamide, and the following formula has been found most satisfactory:—

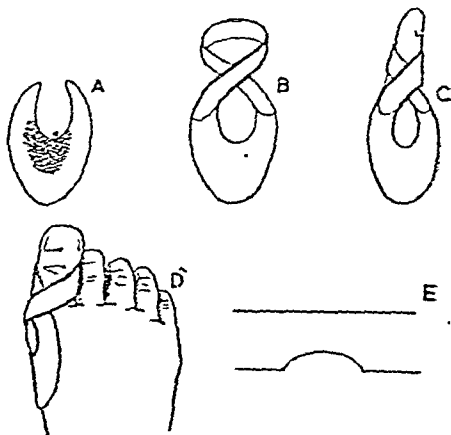
Sulphadiazine (powder)	7½ grains (0.5 g.)
Mucilage Promulsin (2.5 per cent.)	10 minims (0.6 ml.)
Syrup	5 minims (0.3 ml.)
Concentrated spirit of chloroform (20 per cent. v/v)	3/8 minim (0.02 ml.)
Peppermint water	30 minims (1.8 ml.)
Water	to 60 minims (3.6 ml.)

The routine dose for infants under one year is 120 minims (7 ml.) (1 g. of sulphadiazine) initially, followed by 60 minims (3.6 ml.) every six hours. The same dosage is given to "toddlers". Potassium or sodium citrate is given at the same time. It is contended that six-hourly dosage should always be specified for children under twelve years of age. In the case of penicillin, two strengths are used for intramuscular injection: 30,000 units per ml., and 50,000 units per ml., and injections are given every three or six hours, depending upon the severity of the infection. Doses of 300,000 units of penicillin in oil are given daily to children of various ages in the out-patients' department. Oral penicillin is used extensively: 20,000 to 30,000 units for infants, and 30,000 to 50,000 units for toddlers. Paraldehyde by lavage is favoured by E.N.T. surgeons as a preoperative measure; the average dose is: 30 minims (1.8 ml.) for babies of 8 lb. (3.6 kg.); 35 minims (2.0 ml.) for babies of 10 to 11 lb. (4.5 to 5.0 kg.), and 45 minims (2.7 ml.) for babies of 11 to 13 lb. (5.0 to 5.9 kg.). The routine treatment of influenza meningitis in toddlers is: sulphadiazine, 1 g. six-hourly; penicillin, 30,000 to 40,000 units intrathecally every day, and up to 100,000 units intramuscularly every day; specific *H. influenzae* serum, 90 to 150 ml. Very little morphine is used. Phenobarbitone and phenobarbitone sodium are among the most commonly used

drugs. In infantile eczema, ½ a grain (32 mg.) is often given three or four times daily, whilst 3 grains (0.19 g.) of phenobarbitone sodium is given intramuscularly in status epilepticus.

Removable Pad for Hallux Valgus

A REMOVABLE pad for hallux valgus is described by M. E. Endersby (*Chiropodist*, March 1949, 4, 66). A piece of felt of the desired thickness is cut as in fig. A, and pared so as to leave the maximum thickness near the joint (as in the shaded area). Then a strip of 1-inch extension plaster is cut and faced with 1-inch zinc oxide plaster. One end of the extension plaster is fixed to the top corner of the pad on one side and zinc oxide plaster on the other. The double plaster is then twisted into a figure-of-eight and the other ends of the strip are fixed to the opposite



top corner (fig. B). The pad is drawn downwards to fit exactly round the joint, and as this is done the strapping round the great toe tightens and so tends to draw the toe upwards. Slight shaping of the strap where it passes between the first and second toes (fig. E) improves the fit of the pad, which may be held in place either by an elastic band or by a strip of 2-inch zinc oxide plaster. Figure C illustrates the side view of the pad when in place, and figure D the full view.

Tromexan: A New Synthetic Anti-coagulant

THE use of "tromexan", the ethyl ester of 4, 4'-dioxycoumarinyl acetic acid, in a series of 73 cases of vascular affections—thrombophlebitis, plebitis, myocardial and pulmonary infarct, arteriosclerosis—is recorded by R. Della Santa (*Schweizerische Medizinische Wochenschrift*, March 5, 1949, 79, 195). The dosage

employed in acute cases was 1200 mg. daily, in divided doses, two- to four-hourly, decreasing after the second or third day to reach 450 to 300 mg. daily by the sixth day, and thus maintained to the end of treatment, the maximum period for a single course being sixty-two days. Daily prothrombin estimation should be carried out until stabilized at about 20 per cent., when estimation can be made weekly. If strict prothrombin estimation cannot be done regularly a lower dosage scheme should be employed—900 mg. daily, decreasing to 300 mg. The results show 80 per cent. success in thrombophlebitis and phlebothrombosis. The drug is stated to be indicated in cases of threatened embolism, and particularly myocardial infarct. The best results were obtained by early administration as a preventive of post-operative phlebitis and pulmonary embolism. Results in arterial affections were not so satisfactory. Some complications occurred: hæmorrhage (7), hæmaturia (3), and single occurrences of disturbance of vision, sudden appearance of petechiæ, bleeding at the site of insertion of the trocar, mild intestinal hæmorrhage, and epistaxis. Contraindications to the use of tromexan are: advanced cachexia, toxic conditions, hæmorrhagic diathesis, hepatic and renal disease. It is claimed that tromexan is highly soluble and rapidly absorbed, and causes no digestive upsets.

Hexachlorocyclohexane in Scabies

THE use of a vanishing cream of hexachlorocyclohexane in the treatment of 100 patients with scabies is recorded by A. Benson Cannon and M. E. McRae (*Journal of the American Medical Association*, October 23, 1948, 138, 557). The procedure was as follows:—

After careful inspection, and without preliminary bathing, a thin film of the cream (1, 2, 3, 4, 5, 6-hexachlorocyclohexane 1 per cent. in vanishing cream base) was rubbed into the entire skin surface of infants, and from the neck to the sole of the foot in adults. The patient was requested to refrain from bathing or washing the hands for twenty-four hours. Then, after a bath, the patient was directed to use fresh underwear, night clothes and linen. All discarded clothes and linen were to be well laundered before re-use. The patients were re-examined at the end of one week, and other members of the family were examined at the earliest possible moment and treated if necessary.

Of a total of 61 uncomplicated cases in adults, 41 were completely cured after one treatment, and 20 after two treatments. Of five secondarily infected cases in adults, 1 was cured after one treatment and 4 after two. Of 30 uncomplicated cases in children 18 were cured after one treatment, 9 after two, and 3 after three treatments. Of 4 secondarily infected cases in children 1 was cured after one treatment, and 3 after two treatments. No cases of irritation or sensitivity occurred, and there were no contraindications even in the presence of severe secondary derma-

titis. A few cases of pediculosis also responded well.

Magnesium in the Treatment of Dysmenorrhœa

BECAUSE of the experimental and clinical evidence suggesting that magnesium is a uterine sedative, W. J. Rawlings (*Medical Journal of Australia*, January 15, 1949, 36, 61) investigated its action in spasmodic dysmenorrhœa. He used magnesium gluconate in doses of 20 grains (1.3 g.) daily. In cases of premenstrual distress this dose was given daily for seven days before the onset of menstruation and on the first day of the period. For menstrual distress he gave it for four days before the onset of menstruation and on the first three days of the period. All his patients were suffering from primary dysmenorrhœa. Of fifteen private patients with premenstrual distress, five were cured and another eight were relieved but had to repeat the treatment before each period. Four factory patients with premenstrual distress were relieved. Twelve private patients with menstrual distress were treated and all obtained some relief: five were cured, five obtained complete relief, and two received partial relief. Four out of six factory patients with menstrual distress were relieved.

Aureomycin in Primary Atypical Pneumonia

AUREOMYCIN by mouth has been used in the treatment of a small group of patients with primary atypical pneumonia, confirmed by clinical, X-ray and laboratory findings, by M. Finland, H. S. Collins and E. B. Wells (*New England Journal of Medicine*, February 17, 1949; 240, 241). The drug was given in the form of capsules of the crystalline hydrochloride, 1 g. every four to six hours until the temperature became normal for a few hours, and thereafter every six to eight hours for an additional two or three days. In every case the temperature fell to normal, and remained so, within twelve to thirty-six hours of the first dose of aureomycin. There was also loss of toxicity, improvement in the systemic and respiratory symptoms, and no further demonstrable extension of the pulmonary lesions. There was some nausea and vomiting with large doses. In the first twenty consecutive cases treated the patients were essentially well by the eighth or ninth day of the disease. In another case, in which the patient was failing rapidly and the chances of recovery were slight, there was improvement eighteen hours after the beginning of aureomycin therapy and the lungs were clear after two weeks. On

the basis of the results obtained the authors state: "... aureomycin may be said to be highly effective in the treatment of cases of primary atypical pneumonia of the variety that is associated with the development of cold agglutinins".

Dangers of Ingestion of Mineral Oil

THE dangers of ingestion of mineral oil as a laxative over a long period are emphasized by L. Schneider (*New England Journal of Medicine*, February 24, 1949, 240, 284), who gives detailed particulars of five cases of oil pneumonia in elderly patients observed over a period of two years. In one case, a sixty-seven year old man who had been in the habit of taking two or three tablespoonsful of mineral oil almost daily for constipation for twenty-five years, an X-ray examination during a mobile survey showed diffuse conglomerate infiltration in the lower half of both lungs, and examination of the sputum some days after ingestion of oil had ceased, showed it to be thick, greenish, and odourless with the presence of mineral oil droplets macroscopically. As there are no symptoms in the early stages, clinical diagnosis is difficult, but as the condition progresses recurrent acute pneumonia may occur, or the patient may become noticeably dyspnoeic with a hacking cough. Examination of the sputum for the presence of oil drops, and aspiration biopsy of the affected lung shown by X-ray examination, are the most effective measures. Differential diagnosis includes bronchiectasis, tuberculosis, and carcinoma of the lung.

Radiology of the Small Intestine

As a rapid method of radiological examination of the small intestine, S. Weintraub and R. G. Williams (*American Journal of Roentgenology*, January 1949, 61, 45) recommend the use of a barium-normal saline mixture followed by ice-cold normal saline. It is also claimed that this method gives more complete filling of the entire small intestine and a clearer delineation of the mucosal pattern. The method consists in giving the patient 4 ounces of barium and 4 ounces of isotonic normal saline at room temperature. Following examination of the œsophagus, stomach and duodenum, the patient drinks 8 ounces of ice-cold normal saline. Five minutes later an abdominal film is taken, and the patient then immediately drinks another 8 ounces of ice-cold normal saline. Abdominal films are taken ten minutes and twenty-five minutes later. All these films are examined "wet" and any suspicious areas are X-rayed; if the suspension has reached the cæcum, a film is taken of the terminal ileum. If the head of the meal has not

reached the cæcum, additional films are taken at half-hour intervals until it has. In 91 per cent. of 235 normal cases the head of the meal reached the cæcum in one hour or less. In 46 abnormal small intestinal cases "the lesions were as well demonstrated with this method and in several instances were shown to better advantage than with the hourly film method". The physiological basis of this method is said to be the action of a cold solution in relaxing gastric tonus and opening the pylorus. The more physiological action of a normal saline solution, as compared with that of a water solution, is also a factor.

Diabetic Syrups

FORMULÆ for diabetic syrups, quoted from a paper on the subject by M. Woo and C. L. Huyck in the *Bulletin of the National Formulary Committee*, 1948, 16, 140, are as follows:—

(1) Powdered tragacanth	1.5
Glycerin	6.0
Soluble saccharin	0.1
Methyl parahydroxybenzoate	0.1
Distilled water q.s.	100.0

The glycerin is mixed with 75 ml. of water in a tared vessel and heated to boiling. The heat is removed and the tragacanth and methyl hydroxybenzoate added, macerated for twenty-four hours, stirring occasionally. The saccharin and sufficient distilled water to make 100 gm. are added, and the mixture strained through muslin.

(2) Gelloid (purified Irish moss)	1.0
Methyl parahydroxybenzoate	0.1
Soluble saccharin	0.1
Distilled water q.s.	100.0

(3) Gelloid	1.0
Soluble saccharin	0.1
Methyl parahydroxybenzoate	0.1
Alcohol	10.0
Distilled water q.s.	100.0

(4) Gelloid	1.0
Soluble saccharin	0.1
Methyl parahydroxybenzoate	0.1
Glycerin	10.0
Distilled water q.s.	100.0

About 75 ml. of water (and glycerin) are heated to boiling; the gum, methyl parahydroxybenzoate and alcohol (if used) are added. The mixture is left overnight, and then the soluble saccharin is added and the mixture adjusted to volume. (*Pharmaceutical Journal*, November 20, 1948, 161, 342.)

A Prescription for p-Aminosalicylic Acid

DETAILS of a formula for prescribing sodium p-aminosalicylate are given by the Chief Pharmacist of the Brompton Hospital (G. Raine, *Pharmaceutical Journal*, February 12, 1949, 162, 123):—

..	5 g. (or 3 g.)
..	1 grain (15 mg.)
..	5 minims (0.3 ml.)
..	15 minims (1.0 ml.)
Syrup	60 minims (4.0 ml.)
Water	to 1 fl. oz. (28.5 ml.)

The composition of the emulsion of cassia B.H.P. is given as follows:—

Oil of cassia B.P.C.	48 minims (2.8 ml.)
Tincture of quilla	24 minims (1.4 ml.)
Distilled water	to 1 fl. oz. (28.5 ml.)

REVIEWS OF BOOKS

Practical Aspects of Thyroid Disease. BY GEORGE CRILE, Jun., M.D., F.A.C.S. London and Philadelphia: W. B. Saunders Co., Ltd., 1949. Pp. xviii and 355. Figures 101. Price 30s.

GEORGE CRILE was a pioneer of thyroid surgery, one of the first to show that operations could safely be undertaken in Graves's disease. He will be remembered for his advocacy of "stealing the thyroid" unknown to the patient in cases of severe thyrotoxicosis. His son, George Crile, Junior, has written a review of thyroid disease, based on the practice of the Cleveland Clinic. The book is well written and illustrated, and commendably free from elaborate classifications. It can be recommended as a clear and concise review of the whole subject of thyroid disease, and the section devoted to the use of radio-active iodine in diagnosis and treatment contains information not readily available.

Your Hospital: Heritage and Future. BY A. R. J. WISE. With a Foreword by Sir E. ROCK CARLING, F.R.C.P., F.R.C.S., F.F.R. London: William Heinemann, (Medical Books) Ltd., 1949. Pp. xvi and 239. Illustrations 50. Price 15s.

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Bone Marrow Biopsy. BY S. J. LEITNER, M.D. English translation revised and edited by C. J. C. BRITTON, M.D., Ch.B., D.P.H., and E. NEUMARK, M.B., B.S. London: J. & A. Churchill Ltd., 1949. Pp. xii and 434. Price 42s.

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The Renal Origin of Hypertension. BY HARRY GOLDBLATT, M.D., C.M. Springfield, Illinois: Charles C Thomas; Oxford: Blackwell Scientific Publications Ltd., 1948. Pp. viii and 126. Figures 38. Price 15s.

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The Scotman's Food. BY A. H. KITCHIN, M.B., and R. PASSMORE, M.A., D.M., F.R.S.E. Edinburgh: E. & S. Livingstone Ltd., 1949. Pp. v and 88. Figures 10. Price 3s. 6d.

THIS is the nutritionist's reply to Macduff's cry: "Stands Scotland where it did?" Described in the subtitle as "an historical introduction to

modern food administration", it is written primarily for undergraduates and senior school-boys and girls. As such it can be thoroughly recommended. The authors have been particularly successful in reducing technicalities to a minimum and yet at the same time presenting an over-all picture of the nutritional status of the Scots throughout the ages which is commendably reliable. The approach to the subject is well exemplified by the following quotation from the section on "nutrition and health": "If the problem of assessing individual health is difficult, how much more so is that of judging the health of the numbers that make up our community? A further difficulty is presented by the fact that the Ministry of Food is willy-nilly in the centre of party political strife. Champions are not wanting to exaggerate the effects on our health, both of its successes and of its failures. Overstatement is a necessary feature of party politics. The reader is advised to take all statements about the health of the people in relation to their food with more than a grain of salt".

Die Primäre Tuberkulose bei Erwachsenen und Kindern und Ihre Entwicklung. By S. J. LEITNER, M.D. Berne: Hans Huber, 1948. Pp. 157. Figures 32. Price Sw. frs. 15.

THE age of infection in tuberculosis is increasing so that physicians working among adults are now seeing forms of the disease long familiar to paediatricians. This new work deals with primary tuberculosis, based upon 106 children and 160 adults and adolescents seen by the author and traced over a period of two to eight years. He stresses the frequency with which the disease is unrecognized in the early stages, and in answer to those who allege that primary tuberculosis is always benign, produces evidence of a mortality of 12.5 per cent. There is a summary in English but only one reference to work in Great Britain. There is a good series of illustrations but no index. Dr. Leitner's own contributions to the subject are well known, and it is valuable to have them collected, so to speak, into one volume.

German-English Medical Dictionary. By F. S. SCHOENWALD, M.D. London: H. K. Lewis & Co., Ltd., 1949. Pp. viii and 241. Price 75s. 6d.

ALTHOUGH there are several well-known German-English medical dictionaries this new work will fill a niche of its own. The author has taken infinite pains in its preparation by giving typical examples of correct usage for medical purposes. Not only translators, but readers of German and English medical literature gener-

ally, have been provided with a valuable guide by the painstaking labours of the late Dr. Schoenwald, to whom they owe a debt of gratitude.

NEW EDITIONS

Textbook of Medical Treatment, edited by D. M. Dunlop, M.D., F.R.C.P., L. S. P. Davidson, M.D., F.R.C.P., and J. W. McNee, D.S.O., M.D., F.R.C.P., in its fifth edition (E. & S. Livingstone Ltd., 35s.) has been subjected to extensive revision. Three new chapters have been added: on the antihistamine drugs, the treatment of dehydration and hypochloræmia, and the care of old people. Another new feature is the adoption of the metric system of dosage, with equivalents in the apothecaries system in the case of older drugs. A new edition of this well-known textbook of medicine is assured of a warm welcome.

EXTENSIVE revision has been undertaken in the preparation of *Practical Orthoptics in the Treatment of Squint*, by T. Keith Lyle, M.D., M.CHIR., M.R.C.P., F.R.C.S., and Sylvia Jackson, S.R.N., D.B.O., in its third edition (H. K. Lewis & Co., Ltd., 35s.), and particularly in the chapter on heterophoria, in which information gained in the Royal Air Force during the recent war has been incorporated. The new edition is well produced and illustrated.

Malignant Disease and Its Treatment by Radium, Vol. 2, by Sir Stanford Cade, K.B.E., C.B., F.R.C.S., M.R.C.P., in its second edition (John Wright & Sons, Ltd., 52s. 6d.) deals with malignant disease of the mouth, pharynx, larynx and neck, their diagnosis, the choice of treatment, and the technique of radium therapy. The illustrations, many in colour, clearly demonstrate the value of radium therapy in these conditions.

GARROD, BATTEN AND THURSFIELD'S *Diseases of Children*, Vol. II, edited by DONALD PATERSON, M.D., F.R.C.P., and ALAN MONCRIEFF, M.D., F.R.C.P., in its fourth edition (Edward Arnold & Co., 40s.) contains a wealth of new material, among which is a chapter on disorders of the blood, sections on surgery in the treatment of congenital malformations of the heart, penicillin in bacterial endocarditis, the chemotherapy of syphilis and gonorrhœa, and a chapter devoted to malignant disease in childhood. These are but a few items taken at random from this welcome new edition.

Practical Public Health Problems, by Sir William Savage, B.Sc., M.D., in its second edition (J. & A. Churchill Ltd., 14s.), has three new chapters, including one on the investigation of enteric outbreaks. Medical Officers of Health will find much useful information on measures for the prevention of infectious diseases.

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THE PRACTITIONER

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NOTES AND PREPARATIONS

NEW PREPARATIONS

FUNGICIDAL OINTMENT AND POWDER—Boots.—Fungicidal ointment (undecylenic acid 5 per cent., zinc undecylenate 20 per cent., in a vanishing cream base) and fungicidal powder (undecylenic acid 3 per cent., zinc undecylenate 20 per cent., in starch and kaolin base) have been prepared for the prophylaxis and treatment of tinea pedis and other dermatophytoses. The ointment is issued in tubes of 1 ounce, and the powder in sprinkler containers of 2½ ounces. (Boots Pure Drug Co. Ltd., Station Street, Nottingham.)

MAGSILATE aspirin tablets consist of a core of acetylsalicylic acid compounded with sugar and a flavouring agent, with a protective film to prevent deterioration, and layers of magnesium trisilicate, magnesium hydroxide and sugar added. (Westminster Laboratories Ltd., Chalcot Road, Regents Park, London, N.W.1.)

STEROXYL CHOCOLATE DRAGEES each contain 50,000 International Units of pure vitamin D₂ in a chocolate base which renders them palatable and thus easy to administer to children under careful supervision. The dragées are issued in bottles of 25, 100 and 1000. STEROXYL-15 (15 mg. = 600,000 I.U. of vitamin D₂ per ampoule), ORAL in alcoholic or oily solution, and INJECTABLE, has been prepared for massive dose therapy. (Roussel Laboratories Ltd, 95 Great Portland Street, London, W.1.)

NEW APPARATUS

THE CULLEN CRANE has been devised for the single-handed lifting and turning of immobilized patients. The apparatus, which is made in polished duralumin, consists of two uprights supporting a horizontal overhead beam from which a cradle is suspended by webbed belting. The belting passes over the pulleys beneath the overhead beam and leads to a winch on one of the uprights which is operated by a crank handle that permits raising and lowering of the patient by one attendant with great ease. The cradle consists of two parallel rollers, across which lie broad canvas belts. (Cecil H. Cullen & Son, Langford, Bristol.)

OXYGEN TENT EMERGENCY SERVICE

A new depot of the Oxygenaire day and night emergency service for oxygen tents and oxygen therapy equipment has been opened at Cardiff. The service will be available to all hospitals, nursing homes, and medical practitioners in the area (Tel.: Cardiff 1361). Further details of the service can be obtained from Oxygenaire Ltd., 8 Duke Street, London, W.1 (Tel.: Welbeck 1322).

AMERICAN CONGRESS ON OBSTETRICS AND GYNECOLOGY

The fourth American and International Congress on Obstetrics and Gynecology will be held at the Hotel Statler, New York City, from May 14 to 19, 1950. Inquiries concerning the scientific sessions and meetings should be addressed to the Chairman of the Congress, Dr. Fred L. Adair, 24 West Ohio Street, Chicago 10.

NATIONAL LEAGUE OF HOSPITAL FRIENDS

WHEN the hospitals were nationalized last July, local Leagues of Hospital Friends and other bodies with similar aims were formed under the Presidency of Lord Luke. A survey made recently by the British Hospitals Association shows that already some 500 hospitals have between them the benefit of the interest and support of 175 leagues. A Memorandum on the survey is obtainable from the British Hospitals Association, 52 Green Street, London, W.1, price 3d.

PUBLICATIONS

Proceedings of the Annual Meeting of the British Medical Association, 1948, edited by H. A. Clegg, M.B., F.R.C.P., have now been published in a well-produced volume. (Butterworth & Co. [Publishers] Ltd., 35s.)

Proceedings of the International Congress on Population and World Resources in Relation to the Family, Cheltenham, August 1948. (H. K. Lewis & Co. Ltd., 10s. 6d.)

Vitamin A Requirement of Human Adults (Med. Res. Coun. Spec. Rep. Ser., no. 264), compiled by E. M. Hume and H. A. Krebs. (H.M. Stationery Office, price 3s.)

Annual Report of the Institute of Almoners, 1948, is obtainable from the Secretary, the Institute of Almoners, Tavistock House (North), Tavistock Square, London, W.C.1.

Sugars and Bacteria deals with the metabolism of sugars by micro-organisms, the fermentation reactions and classification of bacteria, and various tests. (Thomas Kerfoot & Co. Ltd., Vale of Bardsley, Ashton-under-Lyne.)

B.D.H. Standard Stains.—A new edition of this booklet is now available on application to the British Drug Houses Ltd., B.D.H. Laboratory Chemical Groups, Poole, Dorset.

MEDICAL ASPECTS OF CAMPING

This article on pp. 396-404 in this issue will be available shortly in pamphlet form with buff cover, price 1s, post free, or 10 copies for 9s. and 50 for 40s. Owing to the large demand, the pamphlet *Notes for the Patient with Indigestion*, has again been reprinted. (For particulars see *The Practitioner*, February 1949, p. 172.) The contents of the June issue, which will contain a symposium on "Food Poisoning", will be found on page lxxiv at the end of the advertisement section.

THE PRACTITIONER

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FOOD POISONING

A NATIONAL PROBLEM

By E. T. CONYBEARE, M.D., F.R.C.P.

Medical Officer, Ministry of Health.

THE designation of a particular disease or group of diseases as a national problem needs to be examined critically. The prevalence in this country of the group of diseases known as food poisoning cannot at present be measured accurately enough to show that it is increasing to the extent which some believe or how it compares with the incidence elsewhere. Many who have travelled recently in the United States are impressed by standards of care and cleanliness in the preparation and distribution of food which seem to be so much higher there than in Great Britain. Enough is known about the bacteriology of food poisoning to make it certain that dirty or careless food handling is often a cause of outbreaks, and therefore it is not unreasonable to suppose that prevalence may be unnecessarily high, and even increasing, in this country, where standards of food hygiene are admittedly low and a steadily growing proportion of the meals taken are prepared in the kitchens of canteens and restaurants. A sound enough case for the raising of current British standards in the preparation and distribution of food can, of course, be made on many other grounds, but it is perhaps in relation to food poisoning that the importance of the measures needed to improve food handling can be impressed most easily on the public and also on the catering industry.

It is hoped that in a few years' time the extent to which food poisoning is prevalent in this country will be known more accurately than it is at present; it is possible that the etiology of this group of diseases will prove to be a constantly changing one and that the measures accepted as adequate to deal with it will need to be reviewed regularly. To Government departments, such as the Ministry of Health, the Ministry of Food and their associated laboratory services, belongs the task of collecting and studying information about food poisoning, also of promoting the measures most likely to be effective in prevention and control.

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Nutrition...

THE ANSWER TO MODERN DIETARY PROBLEMS

There is evidence that the reduced daily calorie intake of the nation, resultant upon the lower quantitative and qualitative food standards of to-day, has a tendency to be a contributory cause of asthenia.

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Men appear to die of food poisoning more often than women, the actual figures being 149 males and 97 females for the ten years 1937-46, during which the risk of death from food poisoning at ages over sixty, under five, and thirty-five to sixty years appears to have been ten, nine and eight times respectively what it was at ages five to thirty-five years. This confirms the clinical impression that food poisoning is most serious in the very young and the very old. Food poisoning deaths show a pronounced seasonal peak in the third quarter of the year.

Morbidity.—Although food poisoning has been notifiable since 1938, it was not until the beginning of the present year that the weekly and quarterly totals of notified cases were collected and published by the Registrar-General, and therefore notification does not provide any measure of the general prevalence of food poisoning during the last decade.

About 1927, the Ministry of Health made arrangements for the bacteriological examination at their laboratory in London of material connected with cases and outbreaks of food poisoning. In 1939 this laboratory, together with others, became part of the Emergency Public Health Laboratory Service, which was considerably expanded during the war years, and in 1946 became the Public Health Laboratory Service, of which the constituent laboratories and their associates are now established in 50 centres in England and Wales. Data from the original Ministry of Health laboratory in London and from its successors in the Public Health Laboratory Service have been published in the annual reports of the Chief Medical Officer. These constitute the most useful and important source of information about

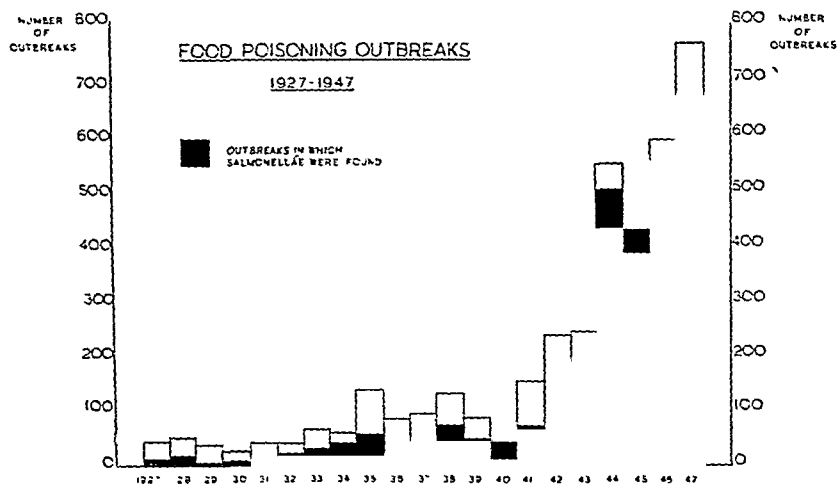


FIG. 1.—Outbreaks of food poisoning during 1927-47.

the prevalence of food poisoning during the last twenty years. The data available from these sources for the years 1927-47 are set out in figure 1.

The unit represented in these data is the "outbreak" of food poisoning

DEFINITION

Most textbooks define food poisoning as a type of acute gastro-enteritis recognizable by the simultaneous illness of a number of persons who have all eaten the same food, and few attempt further classification, except that botulism is usually mentioned as a special type of food poisoning in which a bacterial toxin which affects the nervous system more than the gastro-intestinal tract is concerned.

Section 17 of the Food and Drugs Act, under which food poisoning became notifiable in 1938, does not define it. This is probably wise, since the immediate object of notification is to ensure that the local public health department is made aware as promptly as possible of circumstances which require investigation and may need action of a kind which a general practitioner cannot be expected to undertake. A rigid definition of what is notifiable as food poisoning would defeat this purpose.

In a recent Government memorandum on food poisoning (Memo. 188/Med. Revised, Ministry of Health, 1949) it is stated that cases of notifiable infectious disease, such as enteric fever, scarlet fever or dysentery, conveyed by food should not be notified as food poisoning. A practitioner need not be unduly concerned, however, if the case he notifies as food poisoning turns out after laboratory investigation to be bacillary dysentery. It is clearly his duty to notify any case in which he suspects food poisoning without awaiting the result of laboratory tests; cases of illness due to eating foods inherently poisonous, such as toxic fungi, or to a specific hypersensitivity (allergy) should not, however, be notified as food poisoning.

CLASSIFICATION AND PREVALENCE

Provided that there is adequate investigation, most single cases and a large proportion of the outbreaks of food poisoning can be placed in one of five main categories according to the causative agent concerned, i.e. chemical poisons, salmonella organisms, staphylococci, *Cl. botulinum* and "other bacteria". It is not proposed to attempt to set out here the clinical and pathological basis of this provisional classification. The total incidence of food poisoning and the relative prevalence from these different causes are, however, of some importance in viewing it as a national problem. The chief sources of information bearing on this are as follows:—

Mortality.—During the ten years 1937-46, the Registrar-General recorded a total of 246 deaths from food poisoning in England and Wales, which represent an average annual death rate of about 0.5 per million living. This figure comprises death from all forms of food poisoning and cannot be divided into the five categories mentioned above. Information available in the annual reports of the Chief Medical Officer of the Ministry of Health for the same period, however, make it certain that at least 94, that is over one-third, of the 246 deaths were due to infection with salmonella organisms.

(Food and Drugs Act, 1938), with its provisions for the systematic sampling by public local authorities of food offered for sale, can be relied upon for the detection and prevention of the adulteration or contamination of food by chemical poisons.

Salmonella organisms.—At least two-thirds of the 3,270 food poisoning outbreaks reported between 1938 and 1947 were due to salmonella organisms. Since 1944, the proportion of all investigated outbreaks found to be due to salmonellæ has been about 90 per cent. At present therefore this group of micro-organisms is by far the most important cause of food poisoning.

As long ago as 1925, Sir William Savage postulated that if salmonella infection could be controlled, food poisoning would cease to be a public health problem. From the time when, at the end of the last century, Gaertner first identified a specific bacillus as a cause of food poisoning the bacteriology of the salmonella organisms has become steadily more complicated, and with the latest developments, such as phage typing, has reached a stage at which within an organization such as the Public Health Laboratory Service a special salmonella reference laboratory is essential. Savage thought that the key to the control of salmonella infection lay in the discovery and eradication of the animal reservoirs, from which these micro-organisms were probably spread and often reached human food. Much patient bacteriological and epidemiological work has been done on this subject during the last twenty years, and the resulting literature is now enormous. There has been revealed an astonishing diversity of type within the salmonella group, and an ability of nearly all the member organisms to establish in some animal a harmless carrier state while retaining a capacity to produce disease in other animals of the same or of a different species. Salmonella food poisoning appears, in fact, to be derived mainly from a widespread prevalence of chronic salmonella infection in cattle, pigs, rodents, ducks and other poultry, domestic pets and even human beings. As knowledge of this aspect of the subject grows, the prospect envisaged by Savage of preventing salmonella food poisoning by eradicating the animal reservoirs of salmonella infection becomes steadily more remote. The better course, and indeed the only one, seems to be to interpose between the animal reservoirs of infection and human food anything which will destroy salmonella organisms, or at least inhibit their multiplication. Important in this connexion are careful meat inspection, storage of foods at temperatures which prevent bacterial growth, scrupulous cleanliness in food distribution and preparation, especially when the food is to be eaten uncooked, and cooking times and temperatures adequate to destroy bacteria. Unfortunately, legislation is of little use in setting up such barriers to the transmission of salmonella from animal reservoirs to food. It is futile, for instance, to make the boiling of ducks' eggs for at least eight minutes compulsory by law, or to hope to prevent by regulation the infection of corned

which may comprise anything from one to a thousand or more cases. In the interpretation of food poisoning data the number of outbreaks is of more importance than the number of cases, and for this reason laboratory records are likely to continue to be more useful than enumeration of cases by notification. Taken at their face value the laboratory data set out in the diagram (fig. 1) suggest that by 1947 there had been about a sevenfold increase in the prevalence of food poisoning since 1939, but there are several reasons for thinking that this is not necessarily a correct interpretation. It should, for instance, be noted that in 1939 when the number of reported outbreaks of food poisoning was only 83 the total number of food poisoning deaths was 30, whilst in 1947 with 765 reported outbreaks the number of deaths was only 51. An increased prevalence of the order suggested by the laboratory data is not therefore supported by a commensurate increase in the number of deaths. Since 1939 the number of public health laboratories supplying data on food poisoning outbreaks has grown from less than a dozen to over fifty and, during the same period, the use made by practitioners and public health departments of these laboratories has steadily increased. It is probable that before 1942 a large proportion of food poisoning outbreaks were not reported, either because they were not investigated by bacteriologists or because the laboratories concerned were not part of an organized service. If due allowance is made for the effect of the rapid development of the Public Health Laboratory Service in reducing the number of uninvestigated, and therefore unreported, food poisoning outbreaks, it seems unlikely that the true increase in the prevalence of food poisoning during the war years and after is greater than two- or threefold.

The seasonal peak in the third quarter of the year which has been mentioned above in connexion with food poisoning deaths is also shown by the laboratory data concerning outbreaks.

PREVENTION

It is the prevention of food poisoning rather than its treatment which forms a national problem. To be effective, measures of prevention must be based on adequate knowledge of causes. The classification of food poisoning into five main categories has already been mentioned, and the relative prevalence of these different categories, which can be roughly discerned from the available data, needs to be borne in mind when prophylaxis is considered.

Chemical poisons.—Only ten out of 3,270 outbreaks of food poisoning reported in England and Wales between 1938 and 1947 were due to chemical poisons. Half of this small number were from the ingestion of zinc which was caused by the cooking of fruit in galvanized containers. The remaining outbreaks in the category differed from each other in the particular chemical poison concerned, as well as in the circumstances which allowed contamination of the implicated foods. It appears therefore that chemical food poisoning is a very small part of the whole problem, and that the existing legislation

sonal cleanliness are the temperatures and other conditions under which prepared food is stored pending consumption. Re-heating will not prevent staphylococcal food poisoning because the toxin concerned is heat-stable.

Botulism.—This form of food poisoning is due to a bacterial neurotoxin and is often fatal, but fortunately outbreaks are very rare. Since the well-known Loch Maree incident in 1922, which was the first known outbreak in Great Britain, only seven cases have been reported, with six deaths, all in London in 1935. *Cl. botulinum* apparently needs special conditions in order to multiply sufficiently to produce the toxin which is the cause of the symptoms. The spores of the bacillus are heat resistant but not the toxin, and therefore this disease is not associated with fresh food. The reheating of prepared food is to some extent a protection against it. During the last ten years outbreaks caused by inadequate home sterilization of canned or bottled fruit and vegetables have often been reported from the United States, but notwithstanding the increase in all kinds of home food preservation which took place in this country during the war, no cases of botulism were reported. Nowadays there appears to be hardly any risk of botulism from commercially canned products, and this form of food poisoning has become a medical rarity.

Other bacteria.—In a very small proportion of the investigated food poisoning outbreaks, forming up to now less than 1 per cent. of the total, bacteriological tests have shown that the implicated food had become a culture medium for micro-organisms, such as hæmolytic streptococci or *B. proteus*, which are not ordinarily regarded as pathogenic by mouth. There are clinical features about such outbreaks which enable them to be distinguished from the more frequent salmonella and staphylococcal food poisoning, and the food concerned has nearly always been prepared in the kitchens of communal establishments, such as schools or canteens, where the conditions have been unhygienic or there has been a lack of proper provision for food storage.

CONCLUSIONS

In this country, food poisoning does not cause many deaths and it has not been possible so far to measure accurately the prevalence of food poisoning illness. There is, however, reason to believe that since 1939 the annual incidence of all forms of food poisoning has about doubled.

Food which has become a culture medium for micro-organisms of the salmonella group is now the most frequent cause of a serious food poisoning illness. Food in which certain strains of staphylococci able to produce an enterotoxin have multiplied is the next most frequent cause, but this form of food poisoning is not often fatal. Botulism is the most fatal but the least frequent form of food poisoning. Other causes of food poisoning, including chemical agents, have been comparatively unimportant during the last ten years.

beef, which is to be eaten uncooked after a period of several days, through its being wrapped up in the butcher's shop with the week-end joint of raw carcase meat. The present Food and Drugs Act, with its special regulations relating to milk and to manufactured foods, such as cooked meat, ice cream, and artificial cream, also its provision under Section 13 which makes compulsory a supply of hot water for hand washing wherever food is handled, probably goes as far as is possible or desirable by means of legislation. The big gaps which are left can be filled only by teaching all food handlers, including housewives as well as catering employees, to be scrupulously clean in their methods of preparing and storing food.

The convalescent or chronic human carrier of salmonella infection is a difficult administrative problem. Legal powers are available under the Infectious Diseases Regulations, 1927, to compel carriers of enteric fever or dysentery infection to cease work in connexion with milk production or food handling, but experience does not suggest that any extension of these regulations to include carriers of salmonella infection would be worth while. Persuasion and education appear to be far more valuable in controlling the activities of such carriers than legal powers of compulsion.

Another measure which some advocate for the discovery and control of human carriers of food poisoning salmonellæ is the voluntary or compulsory registration of all food handlers, combined with a systematic and repeated serological or bacteriological examination. When tried out in New York the results of this procedure were not found to be sufficient to justify the time and expense involved and it was very soon given up.

Staphylococcal toxin.—It was not until about 1932 that the heat-stable enterotoxin produced by certain strains of staphylococci was recognized as an important cause of food poisoning. About 5 per cent. of the outbreaks investigated and reported on by laboratories in this country since 1938 have been found to be associated with such staphylococci, and in some years nearly 20 per cent. of all the reported outbreaks have been clinically of the kind caused by staphylococcal enterotoxin. There is reason to believe that this form of food poisoning, although much less frequently fatal than infection with salmonellæ, is the cause of a great deal of minor food poisoning illness which, being transient or symptomatically relatively mild, is not attended by doctors and therefore escapes recognition and investigation.

Chronic human carriers of toxigenic staphylococci in the nose or on the skin appear to be the chief reservoir of infection, and food handlers with septic skin lesions are a particular danger. A great deal can be done, however, to prevent staphylococcal food poisoning if those who handle food in the home or elsewhere can be educated to understand and remember that the personal cleanliness obtainable by comparatively simple means, such as regular hand washing, will eliminate a great deal of the risk. Section 13 of the Food and Drugs Act makes it compulsory in food factories and shops for hot water to be provided for this precaution. Next in importance to per-

THE BACTERIOLOGY OF FOOD POISONING

By G. S. WILSON, M.D., F.R.C.P., D.P.H.

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IN this article I shall use the term food poisoning to denote acute gastro-enteritis coming on soon after the eating of bacterially contaminated food, *not* in the wider sense of food-borne infections, which include such diseases as typhoid and paratyphoid fever, tuberculosis of bovine origin, and undulant fever.

GENERAL BACTERIOLOGY OF FOOD POISONING

Towards the end of last century Brieger put forward the suggestion that food poisoning was due to the presence in the food of toxic amines or *ptomaines* formed as the result of bacterial putrefaction. This explanation had to be abandoned when it was found, first, that most food shown to be responsible for poisoning was perfectly normal in appearance and flavour, and secondly, that putrefied food could often be eaten with impunity. Further observations revealed in many outbreaks of food poisoning an organism belonging to the group now known as *Salmonella*—so called after the American worker Salmon, who described the first member—and for many years it was held that food poisoning was essentially a salmonella infection.

When it became apparent, however, that numerous outbreaks were occurring from which organisms of this group could not be isolated, bacteriologists began to turn their attention to other possible causes. It was then that the enterotoxin of the common nose and skin organism, *Staphylococcus aureus*, was re-discovered and its significance appreciated. This finding was of double interest. It showed not only that food poisoning might be caused by an organism other than *Salmonella*, but that the mode of origin of the two types of poisoning was different. *Salmonellæ* multiply in the intestinal tract and give rise to a true infection, becoming manifest in twelve to twenty-four hours. *Staphylococci*, on the other hand, multiply in the food before it is eaten, producing an irritant toxin which gives rise to symptoms within two to four hours. The first type is now referred to as the "infection" type, the second as the "toxin" type of food poisoning.

More recent studies have rendered it probable that there is a third type falling somewhere between the other two. Thus in some outbreaks from which no salmonellæ or staphylococci can be cultivated, enormous numbers of an organism usually regarded as non-pathogenic, such as *Streptococcus viridans*, *Proteus vulgaris*, or a member of the paracolon, aerobic spore-bearing, or anaerobic spore-bearing groups, have been demonstrated. The

The available mortality and morbidity data on food poisoning show the marked seasonal peak in the third quarter of the year which is to be expected in a group of diseases mainly caused by the growth of certain bacteria which can occur most easily in food at summer temperatures.

The practitioner can do much to assist in dealing with food poisoning as a national problem if he notifies all suspected cases as promptly as possible to the local health department. This will ensure that the data on food poisoning which the Registrar-General has now arranged to collect periodically from Medical Officers of Health will be as accurate as possible, will enable the extensive resources of the Public Health Laboratory Service for bacteriological investigation to be fully utilized, and will give the maximum opportunity for preventive action to limit the extent of the outbreak.

It is important that a large proportion of all outbreaks of food poisoning should be investigated as thoroughly as possible. The work of the Public Health Laboratory Service during the war showed that some of the sudden changes which then occurred in the relative prevalence of the various bacterial strains associated with salmonella food poisoning could be related to the sources of imported foods. The early detection of such changes and their interpretation, as well as the further study of the bacteriology of food poisoning, are functions which the Public Health Laboratory Service should be given every opportunity to perform.

In 1890, Ballard, one of the first medical men to investigate food poisoning in this country, summarized his views about preventing it as follows:—

“The grand precaution of all against food poisoning is the very commonplace one signified by the word *cleanliness*; it should be the business of the conservators of the public health to see that this is observed as well as the duty of every master and mistress of a family”.

These words remain as true to-day as they were over fifty years ago. The author of them was writing at a time when fewer meals were taken in public restaurants, and none in canteens, but his insistence on clean food in the home should still be remembered, for it is there that cleanliness, like charity, ought to begin. Personal cleanliness is more important than environmental hygiene in the prevention of food poisoning, and for this it is necessary to educate rather than to legislate. The doctor, whether as general practitioner, as Medical Officer of Health or as industrial medical officer, has many opportunities to impress on the public the importance of personal cleanliness in dealing with food, and it is in this way that he can best contribute to a solution of the national problem presented by food poisoning.

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- Ballard, E. (1890): *Ann. Rep. Med. Off. Loc. Govt. Board*, p. 202.
Savage, W. G., and Bruce White, P. (1925): *Med. Res. Coun. Spec. Rep. Ser.*, No. 92, p. 48.

SALMONELLA FOOD POISONING

Clinical picture.—Salmonella food poisoning, like typhoid fever or dysentery, is a true bacterial infection. The organisms multiply in the gastro-intestinal tract and produce symptoms after an incubation period of usually twelve to twenty-four hours, although occasionally this may be shorter or longer. The illness is characterized by headache, nausea, vomiting, abdominal pain, and diarrhoea. Fever is usually present, and lasts for two to five days. Nausea and vomiting are not as a rule prominent symptoms, as they are in the staphylococcal type of food poisoning, and they may be absent. The patient is generally better within a week, but a fortnight often elapses before he is really strong again. Occasionally the organisms invade the blood stream and give rise to a fatal infection of the heart or meninges.

Over 150 serological types of salmonellæ have now been distinguished. Before the late war, only 14 different types had been isolated from outbreaks of food-poisoning cases in England and Wales, but following the retail distribution of imported spray-dried egg in 1942, a large number of exogenous types were recognized. Since about 10 per cent. of samples of dried egg were shown to be contaminated with salmonellæ, since the new types of salmonellæ found in food-poisoning cases belonged to the same types and occurred in the same order of frequency as those in dried egg, and since the chronological correspondence between the importation of dried egg and the cultivation of the new types of salmonellæ from cases of food poisoning was very close, the conclusion was drawn that the new types were imported and spread by dried egg. Subsequent observations have merely served to confirm the correctness of this conclusion.

One type of *Salmonella*—*Salm. typhi-murium* (the old *Bact. aertrycke*)—is more common than all the rest put together; it is, in fact, isolated from about two-thirds of all outbreaks. The next most common in order of frequency are *Salm. thompson*, *Salm. enteritidis*, *Salm. newport*, and *Salm. montevideo*. Other types, such as *bovis-morbificans*, *anatum*, *oranienburg*, *tennessee*, *choleræ-suis*, *bareilly*, *meleagridis*, and *potsdam*, are met with not infrequently, and still other types of insufficient importance to mention here are isolated occasionally.

Sources.—In his introductory article, Dr. Conybeare has already pointed out that salmonellæ are pathogenic for a wide variety of domestic animals and birds, and that these constitute the main reservoir of infection for man. Rats and mice also suffer from infection with salmonellæ, and numerous outbreaks in human beings are on record that have been traced to contamination of food from rodent droppings. *Salm. enteritidis* is, in fact, used as a rat poison with the intention of setting up a fatal epizootic. The results are not satisfactory, and sometimes infection is conveyed to man.

It is clear, however, that although animals constitute the primary source of infection a great deal of food poisoning is spread by human agency. Ambulant cases and transitory carriers of salmonellæ appear to be not

inference is that these organisms, which are quite harmless when ingested in small numbers, are able to cause gastro-intestinal irritation when they have been allowed to proliferate abundantly in certain types of food. Whether poisoning results from toxic products in the organisms themselves, or from poisonous substances formed by the breakdown of proteins in the food, or from some other cause, is as yet unknown. The incubation period in outbreaks of this sort appears to be variable, but is often between eight and sixteen hours, that is to say, too long for the staphylococcal toxin type and rather short for the salmonella infection type.

INCIDENCE OF THE DIFFERENT TYPES

Before the second world war it was estimated that about one-third of food-poisoning outbreaks were caused by salmonellæ, one-third by staphylococci, and one-third by other organisms. Experience during the last few years, however, has led to a modification of this estimate. Unfortunately, exact figures cannot yet be given, but of approximately 3,500 outbreaks of food poisoning recorded during the years 1941-48, 90 per cent. were caused by salmonellæ, 3 per cent. by staphylococci, and 2 per cent. by other organisms; in the remaining 5 per cent. either no investigation could be carried out or no bacterial cause could be found.

At first sight these findings would appear to reinstate members of the *Salmonella* group in the position originally assigned to them as being far and away the most important cause of food poisoning; and indeed this is to some extent true. But this conclusion must be modified in the light of further analysis. Thus it is found that 90 per cent. of the so-called outbreaks caused by salmonellæ affected individual persons, and that only 10 per cent. affected groups of persons. On the other hand, all outbreaks caused by staphylococci or other organisms affected groups of persons; no sporadic cases were recorded. The main reason for this difference is that there are great difficulties in detecting sporadic cases of staphylococcal poisoning or of poisoning due to other organisms, so that knowledge of these two types of poisoning is restricted to outbreaks in which usually a large number of persons are affected. It follows that the incidence of the different bacteriological types of food poisoning is probably reflected better by confining attention to outbreaks in the ordinary sense of the term rather than in the narrower sense in which the term outbreak is used to connote any infection, whether of a single person or of a group of persons simultaneously infected from apparently the same source. If this reasoning be admitted, it may be said that approximately 40 per cent. of outbreaks are caused by salmonellæ, 20 per cent. by staphylococci, and 40 per cent. by other organisms. These proportions, it will be seen, are not grossly dissimilar to those quoted before the war. What has happened in the meantime is either that sporadic cases of salmonella infection have become much more common, or that they are now being recognized much more frequently. Probably both are true.

soon after ingestion. The usual incubation period is two to four hours. The attack begins with dizziness, headache, nausea, and vomiting. Abdominal pain may or may not be present, and vomiting is more conspicuous than diarrhoea. The temperature is generally normal or, in the later stages, subnormal. In severe cases the patient vomits continually, is unable to retain his equilibrium, and passes into a state of collapse, in which he lies motionless, with a cold, clammy skin, shallow respirations, and the appearance of impending death. Cases seldom prove fatal, however, and recovery is surprisingly rapid. Many patients are quite well again within twenty-four hours. Subjectively, an attack of staphylococcal food poisoning closely resembles sea-sickness. The patient loses all sense of values, and cares not whether he lives or dies. Second and third attacks may occur, but there is evidence to suggest that some degree of tolerance to the toxin is established as the result of repeated experience.

Sources.—Food becomes contaminated with staphylococci from human carriers. At any time about 40 per cent. of the population harbour *Staph. aureus* in the nose, and a smaller percentage on the hands. The proportion, however, that harbours enterotoxin-producing strains is unknown, but is probably low. Food that is handled by carriers may be contaminated from the nasal spray, although hands are presumably a more frequent source. Persons suffering from staphylococcal skin eruptions on the hands or arms are particularly dangerous.

The mere contamination of the food with an enterotoxin-producing strain of *Staph. aureus* is not sufficient to render the food poisonous. The organisms must multiply abundantly before sufficient toxin is formed to cause symptoms. Opportunities for this are not as common as might be expected. The food must provide a suitable culture medium for the organisms, the temperature must be high enough, the time for which it is maintained must be long enough, and other organisms that multiply faster than *Staph. aureus* or that inhibit its growth must be virtually absent. Thus, it is observed that a given routine may be carried out for months or years without trouble, and not until some change in the circumstances occurs, such as the introduction of a fresh employee, or a sudden spell of hot weather, does the article in question give rise to a wholly unexpected outbreak of food poisoning. In other words, a combination of circumstances must be present before staphylococcal enterotoxin can be formed in food, and the indications are that such a combination is comparatively rare in relation to the number of times in which food is contaminated with staphylococci.

The most favourable vehicles are much the same as those implicated in salmonella infections, namely made-up meat dishes, trifles, layer cakes, custards, and ice cream. In every instance the food is found to have been left for some hours at a temperature favouring bacterial multiplication. Glazed articles, such as pressed beef and brawn, are particularly dangerous,

uncommon, and when employed in the preparation or distribution of food they may transmit infection to other persons. The importance of the human excretor in relation to direct animal sources of infection has still to be defined, but opinion now lays far more stress than formerly on contamination of food from human agents.

Practically any food can act as a vehicle for the transmission of salmonella infection, but the most common articles are those which are prepared in such a way as to enable any organisms that have gained access to them to multiply. Thus, made-up meat and fish preparations, such as pressed beef, brawn, sausages, pies, and rissoles, are often implicated. Ducks' eggs are particularly dangerous, and spray-dried egg, unless eaten soon after reconstitution and thoroughly cooked, is also liable to cause infection. Trifles, ice cream, synthetic cream, and milk figure not infrequently, but freshly cooked meat, bread, vegetables, and fruits seldom act as vehicles of infection. Canned meat is usually sterile but may of course become contaminated after removal from the tin.

Diagnosis.—The bacteriological diagnosis of salmonella infection is best made by isolation of the causative organism from the fæces. During the diarrhœal stage of the disease there is little difficulty in culturing the organisms, but during convalescence the proportion of successful isolations diminishes progressively. Many patients, however, continue to excrete the organisms for two or three weeks, so that a retrospective diagnosis is often possible by examination of the fæces. *Salmonellæ* may often be demonstrated in the fæces of contacts who are perfectly well or who are only mildly indisposed. It is not worth while, as a routine, to examine the urine, nor is examination of the blood for agglutinins recommended except as part of a special investigation.

STAPHYLOCOCCAL FOOD POISONING

Staphylococcal poisoning results from eating food in which staphylococci have grown freely and given rise to their specific enterotoxin. Only *Staph. aureus* seems to be capable of producing this particular toxin, and only some strains of *Staph. aureus* can form it. Not very much is known about the properties of the toxin. It has never been prepared in pure form, and there is no satisfactory animal on which to titrate it. Human volunteer experiments are necessary to demonstrate its presence with certainty. When occurring in food, it has the unusual property of being inactivated more easily by low temperatures than by high. Thus, it may be apparently destroyed by heating to 65° C. for half an hour, although not by boiling for ten minutes. Therefore in the prevention of the disease, reliance cannot be placed on cooking, unless this is very thorough.

The *clinical picture* of staphylococcal food poisoning is often so distinctive as to leave little doubt of the diagnosis, even in the absence of bacteriological investigation. Since the toxin is preformed in the food, symptoms come on

tion of the food and of the patient's excreta fails to reveal the presence of either salmonellæ or staphylococci. The causation of these outbreaks is still in doubt. Clinically, the symptoms tend to be mild and to come on about eight to sixteen hours after the suspected meal. Nausea and vomiting are usually inconspicuous, and neither the abdominal pain nor the diarrhœa is severe. Recovery is generally complete within a day or two. Investigation often throws suspicion on some article of food that has been made up a day or two beforehand and has been left under conditions favourable to bacterial multiplication. Stews, gravies, custards, and trifles are among the most common foods suspected. Bacteriological examination of the patient's vomit and fæces proves negative, but the food itself may show a heavy bacterial contamination with some organism usually regarded as non-pathogenic (see p. 445). No attention can be paid to such a finding unless it is probable that the contamination was present at the time at which the food was eaten; otherwise, it may have resulted from growth in the food left over from the meal. For this reason it is important to take a sample of the food as soon as it is suspected and to keep it on ice unless it can be delivered at once to the laboratory. Whenever the epidemiological findings are clear-cut and the conditions for investigation are favourable, practitioners can help considerably in the elucidation of this form of food poisoning. Volunteer experiments by laboratory workers under such conditions may prove decisive, and already they have shown that some normally non-pathogenic organisms, when present in massive numbers in food, may cause poisoning.

BOTULISM

This disease is discussed adequately elsewhere in this symposium and a full description is not called for here. It is not a gastro-enteritis, and it occurs so rarely in this country that a fuller description is not called for. The most important step in laboratory diagnosis is the demonstration of the toxin in the suspected food.

SUMMARY

Three main types of food poisoning are described:—

- (a) The infection type due to organisms of the *Salmonella* group.
- (b) The toxin type due to the enterotoxin of *Staph. aureus*.
- (c) A third type, intermediate in some respects between the other two, caused apparently by the presence in the food of very large numbers of organisms which in smaller numbers are non-pathogenic when ingested.

Knowledge of the incidence of these three types is very incomplete. Practically all sporadic cases are found to be due to salmonellæ, partly because the difficulty of recognizing the other two types is very great. Of outbreaks in which several persons are affected, however, present information suggests that about 40 per cent. are due to salmonellæ, 20 per cent. to staphylococci, and 40 per cent. to other organisms.

since gelatin affords an admirable medium for growth of staphylococci, and the melted glaze is usually left to cool at atmospheric temperature. In hot weather the conditions are therefore often favourable for the formation of the enterotoxin. Custards, trifles, and layer cakes are often prepared a day or more before they are eaten, and if the degree of cooking is insufficient to destroy the staphylococci present, or if these organisms gain access to the food while it is cooling, abundant growth may occur. More danger attends the preparation of such foods in large quantities than in small, since the rate of cooling is slower. It is probable that for this reason most of the recognized outbreaks of staphylococcal poisoning have followed the eating of food prepared in restaurants, canteens, institutional kitchens, and factories. Domestic outbreaks may, and probably do, occur, but the chances of staphylococcal enterotoxin formation are probably considerably less in food prepared in the domestic kitchen than in kitchens attached to communal establishments. Knowledge on this head, however, is admittedly deficient, since owing to the fact that an attack of staphylococcal food poisoning is of short duration many patients do not seek medical attention. Even if they do, the true nature of their complaint may not be recognized, and because the vomit has been thrown away, confirmation by the laboratory may prove impossible.

The bacteriological *diagnosis* of staphylococcal poisoning is made by the demonstration of *Staph. aureus* in the patient's vomit, or less often in the fæces, and in the suspected food. If the clinical symptomatology is characteristic and *Staph. aureus* is cultivated in large numbers from the food, the diagnosis may be regarded as confirmed. The isolation of this organism from the vomit only, particularly in mild or atypical cases, is less convincing. Interpretation of the findings is especially difficult when the food has been cooked and no staphylococci can be isolated from it. It is generally impossible in such cases to be certain whether the attack was due to the heat-resistant staphylococcal enterotoxin or to some other cause.

Help in deciding whether a given strain of *Staph. aureus* has been responsible for poisoning can sometimes be obtained by determining to which bacteriophage type the strain belongs. It has been found that nearly all enterotoxin-producing strains fall into three bacteriophage types. If the strain is shown to belong to some other type or is untypable, then its etiological significance must be regarded as doubtful. The isolation of the same bacteriophage type from the patient's vomit and from the food is more convincing than from either alone, and if the same type is also isolated from a boil, abscess, ear discharge or other lesion, or even from the healthy skin of one of the food handlers, the chain of causation may be inferred with considerable probability.

FOOD POISONING DUE TO OTHER BACTERIA

Some outbreaks of food poisoning occur in which the most careful examina-

agents from the food and preventing re-infection. In a few cases, e.g. cheese, sauerkraut and wines, the art is selective, i.e., it consists in encouraging the growth of organisms which can bring about certain desirable fermentative changes, and in discouraging those which would cause spoilage.

Preventive measures

The principles underlying the methods for preventing micro-organisms from growing in food are as follows:—

(1) *To increase the concentration of soluble solids* in the liquid phase of any given food, thereby altering its osmotic and other characters so that it no longer constitutes a medium in which micro-organisms can grow. This can be done either by impregnating the food with salt, sugar and edible acids (or a mixture of these) or by removing most of the water from the food and leaving the natural salts, sugars and acids concentrated in what remains.

(2) *Refrigeration and cold storage.*—There is an optimum temperature for the activity of any micro-organism and a progressive reduction in such activity as the temperature falls; hence, spoilage due to micro-organisms is slowed down and eventually checked altogether by cooling. Refrigerated storage is of two types:—

(a) *Cool storage* (often coupled with gas storage) at temperatures above freezing, as used for the temporary preservation of fresh fruits, vegetables, eggs, meat, bacon and cheese. It is hardly necessary to give special consideration to cool storage from the point of view of food poisoning, as the problems here are essentially the same as for fresh foods.

(b) *Frozen storage* at 15° F. (–9.4° C.) or lower: this completely inactivates all micro-organisms.

(3) *Heat sterilization* in hermetically sealed containers. Electronic and supersonic methods are also now proposed for sterilization, but no doubt the problems, from the point of view of food poisoning, would be similar in all three cases.

(4) The addition of small quantities of *chemical preservatives*. These have already been mentioned as being toxic if used in excessive quantities: they check the growth of micro-organisms and are suitable for foods which are either taken in small quantities, often after considerable dilution, or are treated in such a way that the preservative is removed before consumption (e.g. SO₂ is driven off from fruit pulp in jam boiling). There is little or no danger of food poisoning if the preservatives are of the right types and are used in the amounts prescribed by the Ministry of Health, and they need not be mentioned further here.

These four principles can be applied either singly or to supplement each other, e.g. foods like hams, bacon, cheese are cold stored or canned to lengthen their storage life, and fruit pulps, intended for jam making, are preserved with sulphurous acid.

FOOD PRESERVATION IN RELATION TO FOOD POISONING

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ONE of the chief preoccupations of all food manufacturers and preservers is to ensure that nothing of the nature of food poisoning shall follow the consumption of their products. They are well aware that, with modern large-scale production, a single outbreak can cause widespread trouble, not only from the point of view of the sickness and possible fatalities involved, but also from loss of trade and, perhaps, ruin to the particular firm concerned, and from the creation of public prejudice which can affect all firms manufacturing similar foods.

There are two main causes of food poisoning: (a) contamination of food with injurious chemicals, and (b) contamination with injurious micro-organisms which are either directly or indirectly pathogenic, i.e., they either set up irritation in the gut causing illness or, under suitable conditions, they multiply in the food itself, forming toxins.

INJURIOUS CHEMICALS

Chemical poisoning has arisen in the past from faulty ingredients of the food; from contact of the food with poisonous metals or their compounds; from the improper addition of harmful artificial colours, flavours, preservatives, "improvers" and adulterants; and by the purely accidental introduction of some poisonous substance. It is not proposed, however, to deal with this subject at any length here. The laws relating to the degree of contamination with metals and the like which can be tolerated in foods, and the types and quantities of the various substances which may be added, are now precisely defined so as to give ample protection to the public. Also the systems of control, both by official inspectors and analysts, as well as by chemists and technicians in the food factories and in factories producing equipment, wrapping materials, and so on, are such that cases of illness from chemical contamination are now perhaps as rare as it is humanly possible to make them.

MICRO-ORGANISMS

There are many types of micro-organisms, other than the direct and indirect pathogens mentioned above, which cause food spoilage. In fact, the food preserver's art is mainly employed either in creating conditions in or around the food which will prevent micro-organisms from growing and multiplying, even when they are present, or in eliminating all active spoilage

in such a way that when served for eating they will be practically indistinguishable from normally prepared and cooked fresh foods. Probably foods preserved by freezing come nearest to realizing this ideal, but each method has its special advantages and applications. From the point of view of wholesomeness the methods should be considered separately.

Canning.—The danger of food poisoning from canned fruits is negligible. Many of them are too acid for any bacterial growth at all, and in all of them the acid content is too high for the growth of *Cl. botulinum*, the only spore-forming food poisoning organism of any importance. Tomatoes (pH down to 4.3) are near the borderline, but even these can be sterilized for all practical purposes at 100° C.

With the non-acid packs—meat, fish, vegetables and milk—higher temperatures (240° to 260° F. [115.5° to 126.6° C.]) for sterilization are required, but standard processes in pressure cookers have been worked out (Bitting, 1937) for all types of products and all sizes of cans, which are based on the maximum recorded heat resistance of spores of *Cl. botulinum*. That these standard processes provide good safety margins is borne out by the fact that there has not been a case of botulism from factory-canned vegetables since they were first introduced in the United States of America in 1925 and adopted in most other countries. The only cases which have occurred have been with foods canned at home by amateurs, using faulty methods and unsuitable equipment and, even so, it is a fact that errors in practice would be almost always revealed by spoilage from bacteria other than *Cl. botulinum*, which is far from being the most resistant organism in its own group of mesophilic spore-forming bacteria. Except in the case of packs intended for tropical climates it is not necessary, in canning, to aim at absolute sterility (Baumgartner, 1946) in respect to the most heat-resistant thermophilic bacteria but, even if some of these should become active, they are not pathogenic. The chances of achieving sterility in canned foods are greatly increased by strict cleanliness in canning factories to ensure that the initial load of infection in the food is as low as possible. This, and the use of the standard processing technique for any given product, make the chances of botulism arising from commercially canned foods quite negligible.

According to Savage (1939), canned foods caused 51 out of 429 outbreaks of food poisoning from toxins in Great Britain from 1932-37, but he considers that "as regards our food supply generally, canned foods can be accepted as a safe and convenient source and one without any special hazards, nutritional, chemical or bacterial".

Frozen foods.—Frozen meat has long been available and, since there is no growth of bacteria at the commercial storage temperatures, there is no more danger from frozen than from fresh meat. Frozen fruits and vegetables, and even frozen prepared dishes are, however, now growing in popularity and the question naturally arises: "Are they safe?"

METHODS OF FOOD PRESERVATION

The actual methods of food preservation may be classified roughly as traditional and modern:—

Traditional methods

(1) *Salt curing and smoking*, in which the food, generally meat or fish, is impregnated with salt and saltpetre. Sugar is sometimes added and the preservative effect of these is increased by smoking, which partly dries the food on the outside and also impregnates it with certain mild preservatives.

(2) *Pickling*, in which the food (vegetables, fruit, spices) is impregnated with vinegar and salt, or vinegar, salt and sugar.

(3) *Preserving in sugar*, in which the finished products contain from about 68 per cent. (jams) to 75 or even 80 per cent. of sugar (candied fruits).

(4) *Drying by exposure to the sun and wind*, as practised from the earliest times for many types of food. In this case the finished products are quite unsuitable media for the growth of micro-organisms.

(5) Preservation by encouraging *certain desirable types of fermentation*. This is essentially a method of increasing the concentration of edible acids and alcohols in the food until no further growth of micro-organisms is possible under the conditions finally attained.

These traditional processes all impart certain characteristic and desirable properties to the food and, although the products are not necessarily sterile, they are extremely safe and wholesome for several reasons:—

(a) The organisms which are directly pathogenic require a temperature of 37° F. (2.8° C.) for growth; hence they do not as a rule multiply, even if present, on products stored at ordinary temperatures, particularly when, as in the case of cured meats, chilling precedes curing.

(b) Although *Clostridium botulinum*, the organism causing the most deadly form of food poisoning—botulism—grows in suitable media and produces toxin between 20° and 30° C., with a maximum toxin production probably at about 28° C., it grows best in nearly neutral media and is rarely found in media with a pH below 4.5. It is also incapable of growing in solutions containing 8 to 10 per cent. of salt and would be inhibited completely by the quantities of salt or saltpetre, coupled with the low temperatures, used in commercial curing (Yesair and Cameron, 1942). The traditional preserved foods are therefore either too acid or too salt to be suitable media for *Cl. botulinum*.

(c) Preserves like jams and most pickles, chutneys and sauces are cooked in the process of manufacture, whereas cured meats are cooked before being eaten. This heat treatment would usually be sufficient to destroy any toxins and active organisms likely to be present.

Modern methods

Generally speaking, the aim in modern methods is to preserve foods

INVESTIGATION OF AN OUTBREAK OF FOOD POISONING

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ALTHOUGH it is true that the practitioner's legal duty in the investigation of an outbreak of food poisoning is discharged when he conforms with the Food and Drugs Act by notifying the cases, he will no doubt wish to do more, since by so doing he may render a considerable service to the community. The time factor may be vital in an investigation, and whether it is a matter of tracing salmonella-infected ducks' eggs to the farm of origin to prevent further sale, or tracing all the shops to which a consignment of staphylococcal-toxin-contaminated sausage loaf has been distributed, time is of the utmost importance. If then an exact, or even a probable, diagnosis as to the type of food poisoning can be made and a preliminary investigation started locally, while the local health department and public health laboratory are being informed and are starting their own particular methods of investigation, the time lag will be considerably curtailed.

The classification of food poisoning favoured by the Ministry of Health (Memo 188/Med. Revised, 1949) recognizes five groups: chemical, staphylococcal toxin, salmonella, other bacterial, and botulinus neurotoxin. Botulism is excessively rare in this country, and food poisoning from chemicals (heavy metals, galvanized cooking-ware) is only a little less infrequent. Apart from bearing these two groups in mind, the cause of an outbreak can be considered to be staphylococcal toxin, or salmonella organisms or, much less probably, the presence of large numbers of such organisms as streptococci or the paracolon bacillus. The toxin cases show symptoms early, possibly as early as half an hour after ingestion, and usually within six hours; the salmonella cases rarely show symptoms under eight hours and may be delayed to twenty-four hours or longer. An exact history is therefore advantageous, and the sooner the patient is examined and cross-examined on this the more accurate it will be; it is well known how unreliable memory is even a day or so after the event. The patient sometimes guesses the food involved, even though it is likely to have looked, smelled and tasted normally; he may implicate it because it "repeated", and he is often right; but he is also often wrong, and whilst due note should be taken of his own diagnosis it should not be allowed to influence the investigator to the exclusion of other possibilities. Hints on taking a patient's history are given later.

NOTIFICATION

Legally, "food poisoning" is not defined further, the term itself being used for the purpose of making the condition notifiable. This occurs in section 17

Frozen fruits and vegetables are necessarily selected and packed with even greater care than canned foods. Vegetables are scalded and thoroughly washed before freezing, and this minimizes their bacterial load. Freezing does not, however, kill the spores of micro-organisms, but there may be considerable mortality of these during prolonged frozen storage (Tressler and Evers, 1946). The only danger with frozen foods of any kind is in allowing them to stand in the thawed condition before being cooked. They deteriorate fairly rapidly at ordinary temperatures and are excellent media for organisms. It is therefore conceivable that they could become harmful if allowed to stand about for many hours in a warm place; they are, in fact, best cooked up from the frozen state.

Dehydrated foods.—There is no fundamental difference between dehydrated and sun-dried foods: dehydration is merely drying specially selected and, when necessary, partly cooked foods by means of heat from fuel in a specially constructed drying chamber under controlled conditions (Morris, 1947). The only dehydrated food which, so far, is known to have given rise to a few cases of food poisoning is dried egg (Medical Research Council, 1947), of which a varying percentage (from 10 to 30 per cent.) of samples may contain a few salmonellæ (from 1 to 50 organisms per g.). These numbers, however, are far too few to cause food poisoning if the dried egg is properly used. For instance, it should not be allowed to stand for several hours (say overnight) in a warm place, after having been reconstituted, and then be consumed either raw or after insufficient cooking. The best practice is to soak the dried egg and, in fact, all dehydrated foods, no longer than is required for proper reconstitution, and then to cook at once. If this is done, the danger is negligible (Gibbons and Moore, 1944; Gibbons, Moore and Fulton, 1944).

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distribution organizations and methods which have grown up during and since the war. Thus infections from ducks' eggs in shell may be scattered over two or three counties and yet be ultimately traceable to one farm, whilst salmonella infections from dried imported egg may be scattered over the whole country. The medical officer of health is required to report any serious outbreak of disease in his area to the central Ministry of Health; he has, until recently, also been requested to report specifically on each case of food poisoning coming to his notice. This serves to give a country-wide view of the incidence to the medical department of the Ministry of Health, and connexions between cases in different parts of the country may thus become obvious. It is, however, clear that the value of this must depend first and fundamentally upon the accuracy of the original diagnosis and prompt notification to the local medical officer of health.

FIELD INVESTIGATION

The general practitioner can himself track down the source in many cases, and in all cases he can be of immense value in starting investigations. He should prevent any food from being thrown away. It often occurs that the food found eventually to be causal does not at first appear to be implicated and small amounts which have not been eaten are thrown into the dustbin, or given to the chickens, or burned or otherwise destroyed. Scraps of food adhering to tins or jars may be important, and the tins and jars themselves, with their labels, may be important clues in tracing infection.

The practitioner should try and get a specimen of *the vomit*. Vomiting is not invariable, and it is seldom prolonged; it is quite likely to have ceased in a matter of an hour or two, and before the doctor can get to the case. Therefore if he is telephoned or is contacted by messenger and the symptoms given are suspicious of food poisoning he should ask for any vomit to be kept. A similar procedure should be carried out with a *fæcal specimen*. Diarrhœa is likely to go on rather longer than vomiting, but in a matter of hours both vomiting and diarrhœa have often stopped, making a fæcal specimen less easy to obtain. If therefore he cannot get to the case straight away, he should ask for specimens to be kept. If, when he gets there, diarrhœa appears to have ceased, he should take a rectal swab. A *specimen of urine*, although less likely to be of value in diagnosis, may be so in cases of metallic food poisoning, and should be procured. Blood will not be required in the early stages. The practitioner should take with him small specimen jars, obtainable from the local public health department or district laboratory, and if no specimens are procurable when he visits, the jars should be left with instructions to preserve a sample of vomit, fæces or urine at the first available opportunity, and the relatives should be told where the specimens are to be sent.

The practitioner should also act for the time being as the epidemiologist, even if he has only one case of food poisoning; he will probably feel a compelling urge to do so if he has several. By so doing he will save much highly

of the Food and Drugs Act of 1938, and is noteworthy in that it is different in form and in requirements from other notifiable diseases (which are mainly notifiable under the Public Health Acts). Section 17, subsection (1) of the Food and Drugs Act states that:—

“If a registered medical practitioner becomes aware, or suspects, that a patient whom he is attending within the district of any local authority is suffering from food poisoning, he shall forthwith send to the medical officer of health of that district a certificate stating:—

(a) the name, age and sex of the patient, and the address of the premises where the patient is; and

(b) particulars of the food poisoning from which he is, or is suspected to be, suffering”.

There are three points of special interest in this: a case must be notified even if it is only suspected; it must be notified forthwith; and some details of the history should be given. That is the law on the notification of food poisoning, but sending a certificate “forthwith” may quite legally be taken to mean putting it in that evening’s post, the medical officer of health getting it the next morning, or a further day later if Sunday intervenes. This, as will be stressed later, greatly reduces its value as a means of initiating successful investigation, and so the practitioner is urged to report the matter by telephone and to begin local investigation himself.

In a rural area or a small town a group of cases of food poisoning may well be in only one doctor’s practice, or in the practice of a partnership. The food has possibly been purchased at the one village shop which sells that type of food. This sort of occurrence makes early investigation relatively easy, and the practitioner, acting as his own epidemiologist, will quite often have been able to trace the infected food to its source before the local medical officer of health has been able to get started on the investigation. But the large majority of the population live in towns and areas where medical practices overlap, and it may well be that half a dozen cases of food poisoning from eating contaminated food in a local café would, if they were ill enough, have half a dozen different doctors attending them. Six cases showing food poisoning symptoms and occurring in one practice at one time makes the diagnosis blindingly clear, but one case occurring in each of six practices is much more likely to be ignored, or to be put down to indigestion or some other condition. Investigation is therefore not made and the opportunity of tracing the source of the infection is lost. This is sometimes not of great importance, as all the contaminated food may already have been eaten in one small locality, but it may be of high importance when still uneaten food has been sent over a wide area. Prompt reporting to the local medical officer of health when it is reasonably probable that a case of food poisoning has occurred will therefore allow a panoramic view of the area to be taken. This process may need to go a stage further. The distributive pattern of food poisoning cases may be a scattered one over a much larger area, and this has been of increasing frequency with the food

FOOD HYGIENE IN SHOPS AND RESTAURANTS

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SINCE the early days of the late war there has been a phenomenal increase in community feeding. Every factory with fifty or more employees has its own canteen, mid-day meals are served to about two-thirds of all school children, British Restaurants have been followed by Civic Restaurants and other cheap eating places, while the meagre meat ration makes it difficult for the housewife to supply both mid-day and evening meals for her family. As a result, probably about one half of the total population has at least one meal a day away from home. This increase in communal feeding places a great responsibility for the careful handling of food upon the kitchen staffs of restaurants and canteens, since a careless cook in such an establishment may initiate an outbreak of food poisoning affecting some hundreds of people, whereas a careless housewife will do harm only to the members of her own family. Another disadvantage of communal feeding is the hazard of handling food in bulk which often allows greater opportunities for bacterial infection. Thus, a large pot of custard or gravy if prepared some hours before it is used may in the interval become contaminated, and the temperature of this cooling semi-liquid medium may be ideal for bacterial multiplication. Or, again, a joint of beef has to be cooked on the day before use and sliced cold in order to make it go further. The manual handling and the time interval before the meat is served may again allow gross bacterial contamination.

Another outcome of the war has been the great increase in the use of prepared foods, such as meat pies of all description, brawn and jellied meats, pressed and corned beef, sausage meat, and the like, all of which are happy breeding grounds for bacteria. Sometimes these made-up foods are prepared in small shops for immediate sale, sometimes in large factories from which they are distributed to many retailers. They are therefore likely to be handled by a number of people and to be stored under conditions which will encourage bacterial growth. As they are usually not sufficiently cooked again to destroy dangerous bacteria, much less their toxins, the risks attached to the use of such foods must be considerable. This probably explains why in recent years more than half the reported outbreaks of food poisoning, involving two or more persons in separate families, have been attributable to made-up meat dishes. The requirements for the proper handling of food may best be discussed under the following headings—the premises, the food utensils, the food itself, and the food handler.

important time, and will obtain a more accurate story while memories are fresh. A few hints follow:—

Obtain *the history* in detail and put it in writing, paying particular attention to the time of onset of symptoms; it will most likely indicate the meal which was at fault, and may differentiate between toxin and bacilli. Note if the suspected food was normal in appearance and taste; it usually is. Make a list of other people in the house who ate the food but have no symptoms; and any people who are ill but did not eat the suspected food. If no food is particularly suspected find out whether a type of food has been eaten which is frequently a vehicle for food poisoning infections—such as milk or custard dishes, synthetic cream in pastry, ice cream, dried egg, meat pies, glazed meat, sausages, meat paste, or shell fish—particularly if the food has been reheated or has been kept for a few hours in a warm place. Ascertain if the patient, or anyone who prepares food in the house, has recently suffered from an abdominal upset, or a skin crack or sore, particularly near the nose, mouth or hands.

Telephone the medical officer of health as soon as practicable and discuss the case with him. Send your formal notification.

If more than one patient is involved a common origin must be searched for. Take the individual histories carefully and compare them. Find out if those affected have eaten a meal in common, or if they have all eaten a similar type of food. Set out everything eaten within the last day or so and compare the list for each patient. A negative history is not so important: a proportion, it may be a high proportion, of those who eat the contaminated food will not have symptoms. They may have only had a small amount, or the toxin was not uniformly distributed, or they may have a high threshold for discomfort or pain. Whatever the reason, some usually escape. But, positively, all those who have definite symptoms will have eaten the contaminated food. Thus if A, B, C and D have all eaten meat sandwiches and only A and B are ill the meat sandwiches are not exonerated, but if E and F who have not eaten meat sandwiches are also ill then the meat sandwiches are not to blame. The investigator must then concentrate on what A, B, E and F ate in common. Having suspected the type of food, find out whether this food was obtained from the same shop, store, farm, or other source. Try to get samples of any of the food suspected and visit as soon as possible the source from which it was obtained to see if the supplier can add any information; for example, knowledge of other cases, where he got the food, how he or other people prepared it, whether they have had previous illnesses of a similar nature, and so on. Try to find out whether the premises are infested by rats or mice.

Information under these headings, whether positive or negative, will be of great value to the medical officer of health when he continues the local investigations or tries to follow up the clues to the point at which contamination occurred.

Refuse, kept in stout well-made bins with tight-fitting lids, should be removed from the kitchen at the end of the day's work. When emptied the containers should be washed and drained dry, since dirty containers attract flies and vermin.

THE KITCHEN UTENSILS

The essential point about all kitchen ware is that it should be kept clean and free of food residue. If this is done, there is no risk of bacterial growth on crockery and cutlery, or, what is more important, in large food containers. Crockery and cutlery are best cleansed by the two-sink-system. Food scraps are first removed and plates are preferably given a pre-washing rinse in hot water. All utensils are then washed in hot water (temperature around 110°F. [43.3°C.]), containing a detergent solution.

Detergents, or surface-active agents as they are more properly called, should have the following properties—(1) wetting, to wet the utensil evenly; (2) emulsification, to disperse fats; (3) dissolving, to dissolve food materials, principally proteins; (4) deflocculation, to break up solid matter; (5) the prevention of film and scale formation which occurs particularly in hard water; and (6) rinsing, the property of being easily rinsed off.

The inorganic detergent substances in powder form consist usually of a mixture of sodium hydroxide or sodium carbonate, which are good dissolving agents, trisodium phosphate and sodium metasilicate, which are satisfactory emulsifying and deflocculating agents, and sodium hexametaphosphate or similar phosphate, which are good water softeners and form soluble compounds with calcium and magnesium salts, thus preventing film formation. The concentration and proportion of these various constituents will vary according to the hardness of the water and the purposes for which the detergent powder is required. Advice can usually be obtained from the manufacturers. Of the organic surface-active agents, the sulphated alcohols such as "teepol" have good wetting, emulsifying and deflocculating properties and do not irritate the skin. They usually cause foam which, although pleasing to the kitchen worker, is unsatisfactory for mechanical dish-washing machines. Other detergents that are coming on to the market are the cationic compounds, which have both cleansing and sterilizing properties but are antagonized by soap and reduced in activity by particulate matter.

If the kitchen utensils have been properly cleaned in some such detergent mixture, they should be transferred in racks to the second sink containing hot water at a temperature around 170° to 180°F. (76.7° to 82.2°C.). Immersion for half a minute in this hot water will virtually sterilize the utensils, which are then placed on a rack on the draining board, allowed to drain dry without wiping, and stored under cover. If cloths are used for wiping, and this is usually essential with cutlery, they should be boiled at the end of the day to ensure that they are clean and sterilized for the next day's use.

What the hand can do the machine can often do very much better, and mechanical dish-washing machines are now being more widely used. If properly handled with the wash and rinse waters at the correct temperatures, they ensure proper sanitation of crockery and cutlery and save a great deal of labour. The procedure is similar to the two-sink system: food

THE PREMISES

The essential features in premises used for the preparation of food are that they should be pleasant to work in, that they should be kept free of dirt and dust in which bacteria may be harboured and multiply, and that they should be protected against flies and vermin. The premises should therefore be as commodious as possible, well ventilated and well lit, preferably with windows facing north to avoid the heat and glare of the sun. Walls and floors should be smooth and washable and ceilings kept in good repair. Glazed tiles or oil paint make the best wall surface and red quarry tiles or terazzo with rounded corners the best flooring: open shelves and ledges which act as dust traps should be avoided. Instead, there should be covered racks for the crockery, partitioned drawers for the cutlery, and cupboards for pots and pans. A hood and exhaust fan helps to remove and condense steam and so prevent a moisture-laden atmosphere. Tables and draining boards should have metal or enamel tops since wooden surfaces are difficult to clean and foster bacterial growth. Accumulation and dissemination of dust are prevented by damp sweeping and dusting and by frequent washing of floors and walls.

There should be a washbasin in the kitchen with hot and cold running water, soap and clean towels. The ordinary roller towel may be the means of transferring infection, a risk which can be largely avoided by the installation of encased roller towels with a fresh section for each user, or by the use of paper towels. The water closet should be conveniently situated but not adjoining the kitchen and should have in it a small washbasin with the notice "Wash your hands now please" over it.

If the premises are infested with rats and mice, this matter should be reported to the Public Health Department which is responsible for vermin control. It will often happen that a number of adjacent premises are infested, and the breeding places must then be traced so that the vermin can be exterminated on what is known as the "block" system. But vermin can also be discouraged by keeping premises scrupulously clean, with no food remains to which they can get easy access, and with intact flooring. There is some doubt about the propriety of keeping a kitchen cat; it helps to keep vermin at bay but recent evidence suggests that it may sometimes be a salmonella carrier.

Flies either breed in the kitchen or come from an outside source. The invading fly is best countered by the use of screens on kitchen windows and doors to prevent the risk of infection being carried in from an outside source, since DDT or other insecticides do not immediately kill the fly.

For flies already in the kitchen an insecticide such as 5 per cent. DDT in kerosene, should be applied over as wide a surface as possible, e.g. walls, ceiling, lamp-brackets, so as to prevent the fly from alighting on a "safe" area. The spraying should be repeated monthly and care should be taken not to contaminate food, although the insecticides in common use are acutely toxic to man only in relatively large amounts. Other kitchen pests such as cockroaches and steam flies can also be eliminated by suitable insecticides, such as gammexane.

substrate or food in which to grow. If any one of these factors is absent, dangerous contamination of food does not occur.

Thus, a trifle or potato salad kept in a warm larder for six hours may, if it was contaminated with an enterotoxigenic staphylococcus during preparation, cause an outbreak of food poisoning. But if it were eaten at once or stored overnight in a refrigerator, no harm would result. Dried egg may be contaminated with salmonellæ which, however, will not multiply in the powder because the moisture content is less than 10 to 12 per cent. Moreover, the organisms are usually in such scanty numbers that if the egg is used immediately after being reconstituted, infection is unlikely to occur, but if the egg batter is allowed to stand in a hot kitchen for some hours before being cooked, trouble may follow. Again, certain foods, such as fats, bread with its hard crust, acid fruit juices and pickled meats, do not readily support bacterial growth although *Staphylococcus pyogenes* will multiply in a salt concentration of 7 to 10 per cent., and a number of food poisoning outbreaks have recently been associated with staphylococcal contamination of pressed beef.

In the handling of food in shops and restaurants, the cardinal rule must be to avoid the conditions which allow or encourage bacterial growth by which food becomes dangerously contaminated. This rule should be observed particularly with pre-cooked meats or other articles of food which are to be eaten without further heating. Meat pies, brawn, jellied meats, sausages, custard and layered cakes, cream buns and the like, are too often left for hours—or even days—on shop counters exposed to the risk of bacterial contamination from many sources. Meat is often cooked the day before it is to be used, contaminated when sliced cold, and warmed up next day on a hot plate which is often not hot enough to destroy the bacterial growth. Trifles and salads are often made too early in the day and kept in a warm kitchen. The remedy for all these dangerous practices is adequate cool and refrigerator space in which cooked and other bacterially susceptible foods can be stored to prevent bacterial multiplication. Many food shops and restaurants are poorly supplied with refrigerators or cold-rooms and many school canteens have none at all. There is no doubt about the urgent need to make good this deficiency both in public eating places and in private homes. Refrigerators must be used intelligently; they are meant to keep food cold, not to cool it down. Thus, a cooked joint of meat or a pot of gravy which is not to be used until the following day, should be cooled first and then put in the refrigerator. The food inside the refrigerator must be so spaced as to allow a free current of air, and the refrigerator must be cleaned periodically, since some moulds, which although not poisonous taint food, flourish at low temperature. It must also be realized that at refrigerator or even lower temperatures, bacteria are not destroyed but are simply prevented from multiplying.

Kitchen stores should be kept in a cool, well-ventilated room. Flour, cereals and the like should be kept in metal vermin-proof containers on shelves, the lowest of which is 8 to 12 inches from the ground. Vegetables should also be stored on wire racks off the ground where vermin cannot easily get access. Milk is often badly handled in restaurants and canteens. If received in churns, the milk should be kept in a separate cool room, or

remains are first scraped off the plates, which are then put into racks and passed on a conveyer belt to the washing compartment where they are vigorously sprayed with a hot detergent solution. They are then passed into the next compartment where they are rinsed in very hot water and after draining are again stacked without wiping.

More important than ordinary crockery and cutlery is the thorough cleansing of the large food containers in which food may be distributed from a central kitchen, as is often done with school meals. Obviously, if such a container is dirty there will be ample opportunity for bacterial growth when food is placed in it, and school outbreaks of food poisoning have been traced to this source.

These containers should therefore be thoroughly washed with hot detergent solution and then sterilized, either by a jet of steam or by washing with a cold hypochlorite solution. They are allowed to drain dry, since a wiping cloth, if not fresh and clean, may add the germs which the washing and sterilizing have removed.

All kitchen apparatus such as food-mixers and vegetable slicers must also be kept scrupulously clean and free of food residues by washing with hot detergent solution followed by a cold hypochlorite rinse. A recent outbreak of salmonella infection was traced to contamination of a mixing machine with reconstituted dried egg containing salmonella organisms.

Drinking glasses are often washed in a perfunctory manner, particularly in the busy public house, and on examination may be found to be heavily contaminated with bacteria. This problem has been tackled by adding a detergent-antiseptic compound to the washing water which is preferably used cold, and in this way the bacterial content of the wash-water and of the glasses is kept at a low level (Davis and Resuggan, 1947).

As a check on the sanitation of crockery and cutlery, a swab test, in which a moistened swab is rubbed over the surface of plate, cup, fork or spoon and a bacterial count made, has been introduced by some American health authorities. There are technical difficulties in such a test, and perhaps a more reliable method is to sample the bacterial content of the wash-water which, in some restaurants, has been found to have counts as high as sewage (Hutchinson, 1947).

THE FOOD

Food may be contaminated with bacteria from many different sources: the air, dust, kitchen utensils, hands, talking and coughing may introduce them from an outside source or the food may already be naturally infected. Fortunately, most of the bacteria that contaminate food do little or no harm unless, possibly, when present in enormous numbers. Even those that do cause gastro-enteritis need to multiply in order to produce their toxins or poisonous substances or must be swallowed in considerable numbers before they can initiate infection. Exceptions to this rule are typhoid and probably dysentery, in which only a few typhoid or dysentery bacilli are needed to cause infection. The conditions required for bacterial multiplication are an interval of time, a suitable temperature, sufficient moisture and a suitable

Hand washing cannot by itself be expected to prevent the risk of staphylococcal food poisoning. Nasal and skin carriers of pathogenic staphylococci are common, and therefore it would be difficult to avoid contamination of food with these organisms, of which, however, only a few types are apparently capable of producing the specific enterotoxin. Much can be accomplished by reducing to a minimum the manual handling of food which is all too common among food handlers in shops and restaurants. Many recent outbreaks of staphylococcal food poisoning have been traced to careless and often unnecessary manual handling of the incriminated foodstuffs.

There was, for example, a widespread outbreak due to the contamination of a gelatin glaze (covering sausage meat) by the hands of several workers with the glaze at a temperature suitable for bacterial growth (Allison, Hobbs and Martin, 1949); or the outbreak that followed the skinning and slicing by hand of cooked lambs' tongues (Hobbs and Thomas, 1948); or the four outbreaks associated with the processing, with much manual handling, of pressed beef (Hobbs and Freeman, 1949).

It often happens that the carrier of the epidemic staphylococcus has some infective lesion of the hands, arms or face: such lesions and healing scars of minor cuts or bruises harbour many thousands of staphylococci compared with the scanty numbers found on a healthy skin. Therefore any accidental cut, scald or bruise should be reported immediately and treated with a protective waterproof covering which will prevent infection and avoid possible absence from work. Too often kitchen staffs allow these minor injuries to become infected and then disseminate the infecting organism to communal towels, kitchen utensils, dust, and the like, from which the food may become contaminated.

Medical inspection.—The food handler must be encouraged to report any sickness as early as possible, in particular any bowel disorder, sore throat or skin infection, and he should be debarred from handling food during such illness. He must also be told that even after he is clinically well he may still be carrying the infecting organism in his bowel or throat or healing skin lesion, so that if he returns to food handling he must take extra care. On the other hand, regular medical examination of food handlers (including laboratory tests) has been tried and abandoned by American health authorities since any beneficial results were small compared with the enormous amount of time and money expended. It is, however, worth while to take a careful medical history when engaging new staff and to inquire particularly about a history of typhoid or bowel disorder. If the prospective food handler gives a suspicious history or has lived abroad in an area where enteric fever is prevalent, a sample of blood should be taken for a Widal test, including examination for the Vi antibody, the presence of which is particularly associated with the chronic typhoid carrier. A positive reaction is an indication for the bacteriological examination of three or more specimens of faeces at weekly intervals to find if typhoid bacilli are being excreted.

Under existing regulations, the Medical Officer of Health has power to prevent any person suffering from typhoid or dysentery from preparing or

in the cold-room whence it is dispensed into clean jugs or other vessels.

If cooked food and sandwiches must be on display, as in snack bars or railway buffets, they should be wrapped in cellophane, or kept under glass covers. But any kind of coverage will not prevent bacterial growth if the food has already been contaminated. Much is heard about the need for wrapping bread but in fact bread is seldom a proven source of food poisoning despite its large share in our diet.

There is at present no bacteriological standard for foods as there is for milk. Clean food may not always be safe food, but food with a high bacterial content is likely to have been kept too long or under unsatisfactory conditions, and if it is not to be cooked before use, may cause intestinal upset even if it does not contain specific food poisoning organisms. Cooking may not always be an efficient safeguard. Pies or other made-up dishes require prolonged, high temperatures in the oven before the centre of the dish is sufficiently heated to destroy bacteria. Thus, a dish of spaghetti heated at 160 to 170° C. for half an hour had reached in the centre a temperature of only 23° C. (a little more than room heat). Similarly, a duck's egg which may be naturally infected with salmonella organisms may not be sterilized by eight minutes' boiling, although the temperature is raised sufficiently within five minutes of its removal from the boiling water to destroy all contained bacteria.

THE FOOD HANDLER

Whilst food may be contaminated from many sources, man is undoubtedly the most important reservoir of the food poisoning bacteria. Even with the salmonella group whose natural habitat is the domestic animals and vermin, man is often the intermediary so that many more outbreaks of salmonella infection are traced directly to a human case or carrier than to an animal source. Since the bowel is the locus of most pathogens causing food-borne infection, the good social habit of washing the hands after the use of the W.C. becomes an essential practice for the food handler. It may safely be claimed that if hand washing became as automatic as adjusting the dress after use of the toilet, there would be a considerable reduction in intestinal infections. That it is at present far from being a universal custom among food handlers was shown by the finding of faecal *B. coli* on the hands of 8 per cent. of 337 food handlers while at work (Buice *et al.*, 1927). If hand washing is to become a ritual for the food handler, the facilities—washbasin, running water, soap, towels—must be readily available; and since frequent hand washing may lead to soft, sodden skin which is easily injured, a good hand lotion is needed to keep the skin healthy and whole, e.g.:—

Powder of tragacanth	1½ fluid ounces (43 ml.) (dissolved in a few ml. of alcohol)
Oil of lavender	10 minims (0.6 ml.)
Oil of lemon	5 minims (0.3 ml.)
Glycerin	180 minims (11 ml.)
Water	to 1 pint (570 ml.)

The lotion may be thickened, if desired, by the addition of zinc oxide and calamine.

THE TREATMENT OF FOOD POISONING

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Food poisoning in its widest sense may be defined as those diseases which result from the ingestion of food contaminated by noxious agents: these may be certain well-defined bacterial groups and their toxins, constituting bacterial food poisoning. In addition, some foods may be intrinsically poisonous, i.e. fungi and shellfish. Parasitic infections may be conveyed through dirty and impure food, i.e. trichiniasis, amœbiasis, but they are usually not considered as food poisoning and will not be dealt with here. The bacteria of other well-defined diseases may be conveyed by contamination of food, e.g. typhoid and dysentery, and although they may need to be considered in the diagnosis of food poisoning, particularly some types of bacillary dysentery, they too will receive only the briefest mention in this article. Gastro-intestinal allergy is also excluded. Finally, symptoms often identical with acute food poisoning may result from the ingestion of food contaminated with chemical poisons. Here again, although they may require consideration in diagnosis, it is not intended to outline their treatment in this article.

As to bacterial food poisoning, in addition to the presence of the organisms themselves or their spores, it is important to realize that the presence of bacterial toxins, which have persisted after the organisms have perished, may be responsible for the symptoms of acute food poisoning. Food contaminated with living bacteria may cause disease because the organisms survive and flourish in the gastro-intestinal tract or even in the blood stream, as well as by the presence of preformed toxins.

CLASSIFICATION

An etiological classification of the causes of food poisoning and similar or related conditions which require to be differentiated is:—

Contamination of food by bacteria, their spores and toxins

- (a) Staphylococcal and streptococcal enterotoxic organisms.
- (b) Salmonella group.
- (c) *Cl. botulinum* group.
- (d) Typhoid, dysentery.
- (e) Unidentified or unknown food poisoning organisms (Savage, 1932).

Mushroom poisoning and other poisonous plants

- Amanita phalloides* (death cap).
- Muscarine types (*A. muscarina*, *A. verna*).
- Indigestible or decomposing fungi.
- Sprouting potatoes, rhubarb leaves.

handling food; in addition, any person who after examination has been proved to be a carrier of typhoid or dysentery infection may be similarly debarred. There are other regulations applying particularly to dairies and to milk and ice cream, but the present legal powers in regard to the control of infectious diseases among food handlers are probably inadequate.

EDUCATION OF THE FOOD HANDLER

Whilst there are considerable powers under the Food and Drugs Act, 1938, in regard to standards of cleanliness in food shops and restaurants, there is little control over the food handler himself. Better standards of personal hygiene are needed but should be encouraged by education rather than be enforced by law. Recruitment of intelligent staff is the first requirement. All food handlers, from shop manager and canteen supervisor to waitress and domestic staff, must feel that they are important people so far as the public health is concerned and be encouraged in good habits of personal hygiene. Nose picking, finger licking, unguarded coughing and sneezing, and the use of dirty handkerchiefs should be avoided, since these habits all encourage the spread of potentially dangerous bacteria. Nails should be short or at any rate clean, hair should be kept tidy under a cap, overalls should be clean, sensible footwear should be worn, for the food handler is on her feet most of the day, and there should be no smoking on duty. Waiters and waitresses should know the proper way to handle crockery and cutlery and should avoid the use of the general utility tea-cloth which is used one minute to wipe a dirty table and the next to wipe the cutlery.

Managerial and key personnel should know the rationale of food hygiene, and for this purpose courses of lecture-demonstrations such as have been organized by the Central Council for Health Education are useful. There is probably a need for specially trained food sanitarians under the Local Authority whose duty it would be to teach the principles of food hygiene so that high standards of personal and environmental cleanliness can constantly be maintained. The sanitary inspector, despite his many other activities, is a most helpful ally in this educational campaign and can be kept up to date by refresher courses in food hygiene. Much can also be done by the food trades by the establishment of food guilds such as those lately inaugurated at Guildford.

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In *mushroom poisoning*, prevention is better than cure and depends upon the recognition of the edible mushroom (*Psalliota campestris*) from the poisonous varieties. It should first be remembered that the edible mushroom is rather liable to undergo ordinary decomposition if exposed for long, for example, in shop windows, and may, if eaten in this state, give rise to mild indigestion and gastro-intestinal upsets. True mushroom poisoning is almost always due in this country to the highly toxic "death cap" (*Amanita phalloides*) (Birch, 1946). As a cause of food poisoning it is quite rare but yet a very fatal variety. Since early recognition and quick treatment may be life-saving, the practitioner cannot afford to be entirely ignorant of the subject.

The edible field mushroom, *Psalliota campestris*, is usually shorter in height than the poisonous variety, the cap being broader and deeper, and white in colour, whilst the under-surface gills are purplish-brown. This is most important. It has no volva at the base of the stem. "Death cap" is usually a little taller and more slender with a pale yellow or greenish-yellow cap and white gills, and a volva at the base of the stem. It is odourless and peels just as easily as the edible mushroom, and its cut surface does not change colour, but tests based upon these features are fallacious. These points of differentiation cover other allied species of poisonous amanita, except *Amanita muscaria*, which is easily recognized by its bright scarlet cap. It is, moreover, essentially a woodland species associated with beech trees and is not a field specimen.

Shellfish poisoning, due as a rule to the ingestion of mussels and occasionally clams, is best avoided by abstention during the closed season, that is from May to October. Poisonous mussels cannot be distinguished from the non-poisonous variety except by animal tests. The symptoms are due to the presence in the mussels of myriads of dinoflagellates on which the shellfish feed.

CLINICAL PICTURE

The commoner forms of food poisoning have been classified as the mild and toxic types, and the more severe infective type. They are usually acute, self-limited disorders characterized by vomiting and diarrhoea, nausea, and abdominal colic, with or without some degree of fever. The onset of the mild toxic type is usually within two to four hours of ingestion of the food and the duration is short, being over in twenty-four to forty-eight hours; it has no mortality. The more severe form presents the same picture intensified, together with symptoms of circulatory collapse, dehydration, prostration, and occasionally septicæmia. The fever may be more prolonged, lasting for several days or even a week or more. To this picture may be added the more specific nervous signs and symptoms and, rarely, secondary blood, liver and kidney disturbances. It should be mentioned, however, that in the severe botulinus infections signs and symptoms of gastro-intestinal disturbance are by no means always present. The nervous signs and symptoms consist of muscular weakness, disturbance of vision,

Fish poisoning

Mussel poisoning; other shellfish, such as oysters and cockles; mackerel, dried and salted cod.

Chemical contamination

From storage or cooking utensils; copper, tin, lead, cadmium.

Disinfectants and preservatives, e.g. formalin.

Accidental or homicidal, e.g. arsenic, antimony.

FOODSTUFFS INVOLVED

The types of food most likely to give rise to food poisoning are meat and meat products, milk and milk products, i.e. ice cream and cheese, whilst grain and pulses may cause special types, such as ergotism and favism. Home-tinned or -bottled meats, fruits and vegetables sometimes fall under suspicion. Prepared meats, cured ham, various types of meat pastes and jellies, made-up meat dishes, meat pies, pork pies, brawn and sausages, have on different occasions been responsible, the offending organisms being the staphylococcus, the salmonella group, and *Cl. botulinum*.

Milk is a potent source of danger and may convey dysenteric organisms, salmonellæ and staphylococci—contaminated from dirty udders, unclean methods of handling, and infected personnel. The same factors are responsible for outbreaks of mild food poisoning from the consumption of ice cream, and are the common cause of outbreaks of gastro-enteritis in the summer months affecting principally children and infants, but the agent responsible is not always identified. Staphylococcal contamination (Natrige, 1948) has been recognized as more frequent than hitherto believed, and it may well be that unknown and yet to be discovered organisms are present, e.g., in infective enteritis of infants.

PREVENTIVE MEASURES

Since prophylaxis or prevention of food poisoning is really the most important aspect of treatment, no apology is made for a brief survey in an article purporting to deal essentially with treatment.

The need for *scrupulous hygiene* in butchers' shops, cookhouses, bakeries, canteens and personal cleanliness among all who handle food, cannot be over-emphasized. Contamination of food by insect carriers is important in the common forms of food poisoning, as well as in the spread of dysentery, typhoid and cholera. The elimination of vermin, dust, dirty cooking vessels and inadequate and dirty methods of cleansing culinary utensils and cutlery must be appreciated. Hutchinson (1947) has shown the high incidence of potentially dangerous organisms which can be recovered from utensils and samples of washing-up water taken from communal feeding centres. All rats and mice about kitchens should be considered potentially dangerous since the salmonella group infect up to 12 per cent. of them, causing diarrhœa, and their deposited excreta may remain a source of infection, especially to milk and bakery products, for three to four months.

cutaneously, or $\frac{1}{16}$ of a grain (4 mg.) to an infant. This will be effective in a few minutes. A stomach tube may be required to empty the stomach. The procedure would be to use a total of one gallon of water with a tablespoonful of salt dissolved in it, using repeated aspirations of about three-quarters to one pint each time by the simple tube and funnel method. If the patient is semiconscious care must be taken in posturing, so that the risk of inhalation of fluid or vomited gastric contents is minimized. A full dose of magnesium sulphate, $\frac{1}{2}$ to 1 ounce (15 to 30 g.), or 1 ounce (28.4 ml.) of castor oil may be left in the stomach before the tube is removed.

If gastric lavage is considered to be unnecessary a suitable purge should be administered by mouth after the emetic. Again, purging may hardly appear necessary when the patient has had severe and continuous diarrhoea for a day or two, and it may be wise only to give a normal saline colon washout, and to pay attention to the question of dehydration due to fluid loss, as well as to the state of the peripheral circulation. A bismuth, chalk and opium anti-diarrhoeic mixture should be given two hours after the bowel purge in an average case. It may be repeated two- or four-hourly for several doses, a typical prescription would be:—

Tincture of opium	5-10 minims (0.3-0.6 ml.)
Bismuth oxycarbonate	20 grains (1.3 g.)
Powder of chalk	20 grains (1.3 g.)
Glycerin	60 minims (3.6 ml.)
Syrup of tolu	120 minims (7.2 ml.)
Water	to $\frac{1}{2}$ ounce (14.2 ml.)

Compound syrup of camphor, up to a 60 minims (3.6 ml.) dose, may be substituted for tincture of opium in this mixture.

It might be thought that in the staphylococcal and streptococcal forms of food poisoning the ingestion of the slowly absorbed sulphonamides, such as sulphasuxidine or sulphaphthaladine would find a place, but the specific diagnosis can only be made by bacteriological examination, and this is some hours after the acute symptoms—almost invariably mild—have been treated by the usual methods of elimination.

The patient should be kept completely at rest in a warm room with hot bottles applied. Heat to the abdomen may be comforting. Undue early exertion may lead to collapse. The fact that the vomitus and stools are infective must be appreciated and appropriate nursing precautions adopted. Absorption or neutralization of the noxious agents may be facilitated by the administration of powdered kaolin, half an ounce (15 g.) twice a day, or activated charcoal, 20 grains (1.3 g.), two or three times a day. In cases of a more serious character showing signs of collapse, analeptics such as nikethamide, 2 ml. subcutaneously, or caffeine sodium benzoate, $7\frac{1}{2}$ grains (0.5 g.), may be indicated. Severe circulatory collapse will indicate the need for intravenous fluids, such as 5 per cent. glucose in normal saline, three to five pints every twenty-four hours, or possibly greater quantities in very

diplopia, dilatation of pupils, loss of pupil reflexes, headache, dizziness, bulbar symptoms characterized by difficult and painful swallowing, and disturbed respiration. A normal or slow pulse with increased respirations are characteristic of botulism, in which in at least one-third of the cases the initial gastro-intestinal symptoms are replaced by an indefinite malaise with constipation, dizziness and weakness, and prostration. The fact that symptoms are delayed for eighteen to thirty-six hours after ingestion of the contaminated food is an important point in diagnosis. In the more common staphylococcal and salmonella food-poisoning group the symptoms of gastro-intestinal irritation tend to develop relatively quickly, two to six hours after ingestion.

In the two main types of mushroom poisoning, "death cap" and muscarina varieties, the symptoms are either gastro-intestinal with collapse and great thirst or, in the latter, largely nervous, but the picture may be complex and has been classified according to the predominant symptoms into gastro-intestinal, choleraic, cerebral and hæmolytic. Since there may be difficulty in distinguishing between the various fungi when confronted with a case the general principles of emesis and purgation should be applied to all. The same principle also applies to the comparatively rare forms of shellfish poisoning, in which the gastro-intestinal, nervous and paralytic symptoms may or may not be associated.

TREATMENT

Fortunately, the successful treatment of food poisoning does not depend upon an accurate knowledge of the cause. There is much that can be done, and done quickly, before a final diagnosis is made. Accurate bacteriological diagnosis must usually wait upon investigation, yet there is urgency with regard to treatment. The practitioner may need to anticipate, he may need to consider what ought to be done upon the assumption that a certain diagnosis will be the probable outcome.

The gastro-intestinal tract should be evacuated at once, and most physicians would begin treatment by inducing emesis or by instituting gastric lavage. In mild cases when time has been lost these procedures lose something of their point, and in the serious delayed cases, such as botulism, their value is dubious. Nevertheless, if there is any doubt at all such treatment should be undertaken. If the patient has already vomited profusely, simple stimulation of the pharynx after swallowing a pint of hot water may suffice to induce vomiting. Otherwise, two tablespoonsful of common salt in half a pint of warm water, or a teaspoonful of mustard in a tumbler of warm water, are remedies that will be readily available. An ounce of tincture of ipecacuanha or powdered ipecacuanha in water, or zinc sulphate, 30 grains (2 g.) in water, are alternatives. In an adult without signs of collapse, apomorphine hydrochloride, $\frac{1}{10}$ of a grain (6.5 mg.), may be given sub-

myoneural junction. The mortality rate in botulinus poisoning is estimated at roughly two-thirds of all cases.

In *mushroom poisoning* the symptoms of gastric irritation come on early, that is, in one and a half to two hours, although occasionally they may be delayed for six hours or more. The same procedures for immediate elimination by emesis, gastric lavage and purging should be adopted. The nervous symptoms of sweating, salivation, convulsions, occur early in the muscarine types, for which atropine is almost a specific antidote, and $\frac{1}{50}$ of a grain (1.3 mg.) should be given intravenously to an adult, and subsequently every four hours subcutaneously, regardless of the species of mushroom involved. Analeptics, such as nikethamide or caffeine sodium benzoate, may also be required; glucose by mouth or per rectum or intravenous drip should be given. All persons who have partaken of the same meal should have the eliminative gastro-intestinal treatment, including a gastric washout. When symptoms of mushroom poisoning are delayed for eight hours or more, being suggestive of death cap poisoning, the same eliminative treatment should be instituted. Active treatment to combat potential liver cell failure, or cholæmia, which may result in collapse and death in at least half the cases, should follow at once. The patient is given glucose and saline by intravenous drip, with insulin, 10 units to cover every 50 g. of glucose, whether by mouth or parenterally. A 10 per cent. solution of calcium gluconate is given four-hourly by intramuscular injection, and vitamin K, 10 mg. daily, and vitamin B, 30 mg. daily, both by injection. The possible need for blood transfusion should be borne in mind throughout treatment and sedatives may be indicated when restlessness and delirium are present, using, for example, pentobarbitol sodium, $\frac{3}{4}$ to 1½ grains (0.05 to 0.1 g.) intravenously, or morphine, $\frac{1}{2}$ of a grain (16 mg.) subcutaneously. The use of antiphallinic serum should be seriously considered; it has been difficult to obtain in this country. Application may be made to the Central Public Health Laboratory, or to the Pasteur Institute, Paris, for "serum anti-phalloïden"; the dose of the particular batch of serum will be indicated, and it is administered intravenously and intramuscularly. A form of treatment based upon the immunity of the rabbit to "death cap" poisoning may be mentioned. It consists in the feeding to the affected patient of minced, uncooked rabbit stomach and brains for several days (Limousin and Petit, 1932).

Milk poisoning.—The so-called "milk poisoning" is due to milk obtained from cows poisoned with white snake root, and corresponds in humans to the "trembles" in animals. The symptoms are weakness, vomiting, pain and thirst. The toxin produces hypoglycæmia; hence after general elimination glucose by mouth or by the intravenous route is especially indicated.

According to Alvarez, *sprouting potatoes* may cause symptoms of acute gastric irritation with mild nervous symptoms of bulbar type and visual disturbances. Rhubarb leaves have been mistaken for spinach and have caused

dehydrated patients. In exceptional cases plasma or blood transfusion may be required.

All food is withheld for the first twenty-four hours. Glucose water flavoured with fruit juices, or very weak tea, may be permitted. Champagne is useful as an anti-emetic in the early stages after the initial treatment. Thereafter, liquid food, soup, milk, beef tea and thin gruel may be added. An important principle is the very slow building up of the diet over a number of days. It has been shown gastroscopically (Schwartz, 1946), in man and in animal experiments, that considerable mucosal changes affecting the digestive and absorptive functions of both stomach and bowel persist for a considerable time after an attack of food poisoning. Hence a too rapid return to a full diet may result in prolonged indigestion and bowel irritability. At a later stage a test meal might indicate whether or not the normal acid secretion has returned. Achlorhydric diarrhoea has been reported following food poisoning.

Recovery from staphylococcal food poisoning may be obvious in twenty-four hours; salmonella infections are rather more severe and may be prolonged for several days, during which time there may be fever. Occasionally, fulminating cases may have a fatal issue. The mortality in salmonella infections ranges from between 1 to 2 per cent.

Cl. botulinum poisoning requires some additional comment. Similar principles of gastro-intestinal elimination apply, but as a rule when the diagnosis is made by the appearance of cerebral symptoms, and especially in a solitary case when suspicion may not have been aroused, prognosis is very grave. The specific antitoxins to the common A and B types of botulinus infections are available through the Public Health Laboratories Service. After preliminary testing of the patient for sensitivity, 50 ml. should be administered intravenously as soon as possible, repeating the same dose every six hours. A continuous mode of intravenous administration has been recommended by Watson (1939) to meet the assumed continuous absorption of toxins from the gastro-intestinal tract, so long as they remain there. Little can be expected from late administration of antitoxins.

Every effort must be made to protect a patient from fatigue, he should be nursed in a warm darkened room, all visitors excluded, various stimulants, such as rectal coffee, subcutaneous nikethamide, ephedrine, benzedrine, as well as oxygen, especially if cyanosis appears, may be called for. The thick mucus accumulation in the mouth requires to be constantly removed with a swab or suction, and may be rendered less tenacious by administration of pilocarpine, $\frac{1}{32}$ of a grain (2 mg.). This drug should be used only if there are no pulmonary complications. The development of pneumonia is a permanent danger and respiratory death follows. The early use of oxygen by mask or tent would do much to reduce this most serious hazard. With these possible dangers in mind the use of morphine is advocated by those who believe that it delays the fixation of the botulinus neurotoxins at the

THE DOMESTIC FOOD POISONING PROBLEM

By A. B. STEWART, M.D., D.P.H.

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THE problem of food poisoning in the home is *mutatis mutandis* similar to the problem of food poisoning experienced elsewhere, but there are certain points of variation. These special points will be discussed in the course of this short article and emphasis placed upon certain aspects of the problem. Any discussion of the domestic food poisoning problem is bound to take into consideration aspects of the general problem dealt with elsewhere in this number. So far as possible these aspects will be touched on lightly and due emphasis given to the domestic aspect of the problem.

The expression "food poisoning" is used here in the accepted and limited sense of the term. Several diseases which may be caused by contaminated food, e.g., the enteric fevers, the dysenteries, and leptospiral jaundice, among others, are excluded from discussion. Perhaps the main differentiation between the type of case usually defined as food poisoning, and those which are not, is the sudden and immediate onset within a short time of eating the infected food in the case of the former, and the relatively long incubation period in the case of the latter.

CAUSAL FACTORS

Food poisoning in the home due to the ingestion of articles which are poisonous in themselves is not particularly common in this country. The wide publicity which is given to mistakes with mushrooms, the inclusion of rhubarb leaves in salads, and the eating of poisonous berries, may be the reason why such accidents are comparatively rare. Poisoning from shellfish is not particularly a domestic problem, but botulism is. We have been particularly fortunate in this country in our experience of botulism, but it is a cause of food poisoning which must constantly be borne in mind. Our innate conservatism in the choice of foods may be another reason why we are saved from more frequent disaster.

In the home the risk of poisoning from *metal impurities* in food containers is small. Cheap enamel or galvanized utensils may give rise to chemical food poisoning, especially when foodstuffs of an acid nature are contained in such vessels. The majority of the recorded cases of such poisoning have occurred when galvanized or enamelled pails have been used in the preparation of food on a large scale. The practitioner is more likely to meet with accidental or intentional chemical poisoning when chemicals of a poisonous nature have been introduced directly into the food at the time of

acute gastro-intestinal irritation due to their oxalic acid contents. Eliminative treatment is indicated in both of these.

Shellfish poisoning.—The treatment of shellfish poisoning, the symptoms of which develop within 30 minutes after ingestion, with tingling of the lips and mouth proceeding to paralytic symptoms affecting the neck muscles, and sometimes those of the limbs, should be adapted to the same principles of elimination of the alimentary tract as for immediate and urgent treatment. Respiratory distress may be severe and the need for artificial respiration may be obvious.

CHEMICAL CONTAMINATION OF FOOD

The accidental contamination of food with chemical poisons may arise in many ways. Acid substances may dissolve lead, copper and cadmium from the containers lined with these metals. Methyl chloride used in some refrigerator systems may leak into foodstuffs. Sodium fluoride, used as an insecticide, may be mistaken for normal ingredients used in cooking, such as baking powder or dried milk, and so cause acute gastro-intestinal symptoms.

Arsenic and antimony salts may contaminate food, being added by accident or possibly with deliberate homicidal intent. Here too, symptoms of acute gastro-intestinal irritation are prominent and severe. The scope of this article does not permit further discussion of them; it will be sufficient to remind the practitioner that they are apt to occur in circumstances similar to those of bacterial food poisoning. Suspicion in such cases will be enough to lead to the special methods of laboratory investigation resulting in their detection.

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cupboards with ventilation to the outer air. Those who are fortunate enough to possess one may use a refrigerator, either as a supplement or as a substitute for the food cupboard. The layout of the kitchen premises themselves may be an important feature in the efficiency of the food preparation in the home. Adequate means of refuse disposal, conveniently placed sinks, as well as the provision for food storage, all are important. In this connexion dustbins with properly fitted lids are important, being of value in the suppression of the domestic fly nuisance. The salvage of food scraps for pig food, which may have merit, is certainly an additional public health problem which the housewife has to tackle. The existence of household refuse, pig food, and indeed any food stores not properly protected is a source of attraction for rats and mice—a subject to be mentioned later.

One of the housewife's problems is the prevention of *contamination of food* which has been left over, or food awaiting reheating, or food prior to cooking. Food in any of these three forms may provide an excellent cultural medium for organisms which may be already present, e.g. reconstituted dried egg left to stand, or for organisms introduced by either human or animal agency at this stage. Foods which are especially liable to contamination include made-up meat dishes, that is, pies, rissoles, and similar preparations, also milk products of any kind, including artificial cream.

The question of human contamination has already been mentioned, and in addition there is the danger of *contamination by rats and mice*. Infestation with rats and mice is a potential source of danger, and contamination of stored foodstuffs by rats and mice is a common cause of bacterial food poisoning. At the present time the occupier of a building is responsible for maintaining the premises clear of rats and mice. He can expect every assistance from the local authority, but he is liable for any expense incurred. The Prevention of Damage by Pests Bill at present before Parliament will place the responsibility on the local authority, but it will remain the duty of the occupier to notify the local authority of infestation. Considerable advances have been made in the suppression of rats and mice as the result of work carried out during the war. Experimental work has given a clearer picture of the habits of rats, and the Ministry of Food has been active in ensuring that recent advances in technique are now readily available throughout the country. Briefly the method used is to incorporate a chemical poison, for example, zinc phosphide in a wheaten base. In the case of rats it is necessary to lay harmless bait for a few days until the rats become accustomed to the presence of the bait; then the chemical poison is added. In the case of mice it is unnecessary to include any preliminary preparation. An important part of this work is to ensure that the drainage system is efficient. It is common for rats to use disused and broken drains as runways.

DOMESTIC HYGIENE

That there are not more outbreaks of domestic food poisoning is a tribute to

preparation. The most common cause of error is failure to label properly powders kept in the kitchen. It would appear that almost any white powder is liable to be mistaken for baking powder by the housewife.

As with food poisoning elsewhere, *bacterial contamination* of food and the subsequent multiplication of the organisms, or the production of toxin, is the most common cause of food poisoning to be met in the home. Elsewhere in this number the diagnosis and the treatment of food poisoning is discussed, but there are features met with in the domestic field which present a contrast with those encountered elsewhere. The outbreak is confined to those in the family circle and to close friends. The circumscribed nature of the trouble is of some assistance in tracing the cause. The food consumed is likely to be similar in each case, and it is unlikely that extensive menus will require checking, or that a large number of persons will require questioning. On the other hand, there is greater likelihood that all the suspected food has been consumed, and it may well be that all the food containers have been cleaned and that little evidence remains to assist in diagnosis. The practitioner can obtain ready help in the investigation of such an outbreak. Since 1932, food poisoning has been compulsorily notifiable in London (Section 7 of the London County Council General Powers Act, 1932), and in England and Wales since 1938 (Section 17 Food and Drugs Act, 1938). There is similar legislation both in Scotland and Northern Ireland. The practitioner can thus rely on the medical officer of health and his staff to take up the investigation, and to have ample laboratory facilities, including the Public Health Laboratory Service now made available throughout England and Wales by the Ministry of Health.

POINTS FOR INVESTIGATION

Carriers.—In any investigation of food poisoning in the home the person responsible for preparing the meal is necessarily suspect as a potential carrier of disease. In addition to the ordinary routine investigation to ascertain whether the food preparer is an intestinal carrier or not, the possibility of a staphylococcal infection must be borne in mind.

Other items which require consideration at this stage include the purity of the *water supply*. In modern urban life the water supply is seldom found to be at fault, but it must be remembered that water which may be delivered in the pure state to the house may at any stage thereafter become contaminated. The purity of the water supply is a thing taken for granted in most built-up areas. In the course of time the provisions of the Water Act of 1945 should make these remarks apply also to water supplies even in remote rural areas.

Another item requiring investigation in the domestic field is the provision of adequate *food storage accommodation*. To-day the provision of adequate food storage accommodation is regarded as an essential of any house fit for human habitation. Provision for food storage should take the form of

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cupboards with ventilation to the outer air. Those who are fortunate enough to possess one may use a refrigerator, either as a supplement or as a substitute for the food cupboard. The layout of the kitchen premises themselves may be an important feature in the efficiency of the food preparation in the home. Adequate means of refuse disposal, conveniently placed sinks, as well as the provision for food storage, all are important. In this connexion dustbins with properly fitted lids are important, being of value in the suppression of the domestic fly nuisance. The salvage of food scraps for pig food, which may have merit, is certainly an additional public health problem which the housewife has to tackle. The existence of household refuse, pig food, and indeed any food stores not properly protected is a source of attraction for rats and mice—a subject to be mentioned later.

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DOMESTIC HYGIENE

That there are not more outbreaks of domestic food poisoning is a tribute to

the cleanliness and endeavour of housewives as a class. During the war years the housewives faced the same handicaps as those that faced the restaurant keeper. Scarcity of towels and soap was a familiar complaint. We still have with us the problem of too little soap, especially in hard water districts. The alarming rise in the number of food poisoning outbreaks was attributed to the increase in communal feeding and to lower standards of food inspection and handling. Personally, I do not believe that the food inspector has knowingly reduced his standards. Other factors which may contribute to the increased notification of food poisoning include a greater awareness on the part of the medical profession, coupled with greater availability of laboratory services. The problems of communal feeding are not the concern of this short article but obviously they contribute to the increase. A common complaint regarding restaurant crockery, that it is often badly cracked and chipped, is one which may also be made regarding domestic crockery. Although evidence has been produced to show that cracked and chipped cups and saucers have high bacterial counts, it has not been demonstrated that disease has been transmitted in this way.

It is pertinent to note that the rise in the number of outbreaks has coincided with the soap shortage. When the Minister of Food finds it possible to increase the soap ration it may be necessary to have second thoughts concerning the reason for the increase in the number of food poisoning outbreaks. Admittedly, soap substitutes are available, but they are expensive and often are not used in the proper way to give the best results. There are several commercial detergents now available which are being used on a commercial scale for cleansing glassware and crockery, but they are probably unnecessary in domestic use. Although there seems little danger of undue emphasis being placed on the cleanliness of dishes, cups and saucers, it is the duty of Public Health Authorities to insist on the importance of the cleanliness of the persons handling the food, and the education of all food handlers in this matter is of prime importance.

CONCLUSION

The domestic problem may be summarized thus: The prevention of food poisoning in the home requires first, a pure food supply. This is a matter very largely in the hands of the Ministry of Food. The provision of adequate kitchen premises is a matter for planning which is being dealt with adequately in new premises—indirectly by the Ministry of Health through the local authorities. The provision of adequate cleaning materials is again a matter which the Ministry of Food controls. Lastly, the adequate training in the domestic field of the housewife is a most important matter, an intelligent approach being perhaps the most important factor in overcoming domestic difficulties of this nature. This is a matter which would appear to be mainly the concern of the Ministry of Education.

HEADACHE

By SIR CHARLES SYMONDS, K.B.E., C.B., D.M., F.R.C.P.

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HEADACHE is of all pains the most difficult for the patient to describe and for the doctor to interpret, and it is only within recent years that any methodical inquiry has been made into the possible sources of pains in the head. So far as is known the afferent nerves concerned are the fifth, ninth and tenth cranial nerves and the second cervical nerve. Anatomically speaking, the most simple examples of pain in the head are those due to the direct affection of these nerves by disease, with pain of appropriate distribution. The headache and suboccipital pain of meningitis are probably of this origin.

CAUSAL FACTORS

Referred pain from disease of parts supplied by peripheral branches of these nerves, and especially the fifth, is of relatively common occurrence. Thus, pain experienced widely in the distribution of the ophthalmic division may be caused by disease of the eye, as in glaucoma; inflammation and engorgement of the turbinates and the channels of outflow from the nasal sinuses cause pain referred mainly to the area of the second division but spreading into that of the first; inflammation in an upper pre-molar or molar tooth may result in pain referred to the eye, the orbital ridge and the temple, and from a pre-molar or molar tooth in the lower jaw pain may be referred to the area over the zygoma and the temple. All the tissues of the scalp are pain-sensitive and when diseased may be responsible for headache, which, having a central focus corresponding to that of the lesion, may radiate widely. Among the extracranial tissues the walls of the arteries are pain-sensitive, especially to stretching; hence inflammation, loss of muscular tone, or raised internal pressure in these vessels may cause headache. Temporal arteritis, migraine, and some of the headaches of arterial hypertension are explained thus. The muscles of scalp and neck, if subject to excessive and prolonged contraction, register aching pain, and are responsible for most of the headaches associated with eyestrain and with the psychological tension of anxiety states. The intracranial structures are mostly insensitive, but the exceptions are important. Stretching or distension of the meningeal arteries causes pain, although the parietal dura is itself insensitive. Pressure upon the tentorium and falx may cause pain, as also traction upon the basal dura where it is adherent to bone. Traction upon the basal arteries or the venous tributaries of the dural sinuses is painful: thus dislocation of the intracranial contents by an expanding lesion causes headache. Increased intra-

cranial pressure does not in itself cause pain, as may be proved by painless increase of pressure by intrathecal injection of saline to twice or thrice the normal level, and the existence of papilloedema and a high cerebrospinal fluid pressure in patients with cerebral tumour who have no headache. Distension or inflammation of the intracranial arteries is painful. Hence loss of tone in their walls with increased amplitude of pulsation will cause headache, and this is the probable explanation of febrile headache and of toxic headaches of reflex origin due to vasodilatation from distension of the hollow viscera: for example, the headache of constipation. The intermittent headache of congenital intracranial aneurysm can also be explained as the result of occasional expansion of the sac.

Some of this information has been derived from the observation of surgeons operating within the skull under local anæsthesia, and a good deal of it from measurements of the amplitude of pulsation in extracranial and intracranial vessels during headaches occurring naturally in migraine and arterial hypertension, and induced experimentally by histamine or artificial pyrexia. Thus, although there is much still to be learned about the causation of headaches, the problem can be approached with some knowledge of the anatomical and physiological mechanisms involved.

THE CLINICAL APPROACH

There are certain questions which must be asked of all patients suffering from headache, and if answers can be obtained the analysis in many cases will indicate the probable diagnosis.

(1) *The setting of the headaches in time.*—This I put first because questions in this direction are as a rule most productive. What is the duration of, or liability to, headache? Is it continuous or intermittent? These questions are closely related and will give information of a kind which will generally reveal two of the most common types of headache met with in practice—migraine, and the headache of depression or anxiety states.

Intermittent headache lasting for hours at a stretch, with intervals of complete freedom for several weeks, and with a history of several years, usually indicates migraine. Continuous headache over a period of weeks or months almost always means a psychological disorder. Headache occurring in the early morning with daily or almost daily frequency and with a short history suggests an intracranial tumour.

(2) *The character of the headache.*—The headache of migraine and most organic diseases is described in terms of what we usually understand as pain, throbbing, aching, stabbing, bursting, and the like. The patient suffering from depression or anxiety will describe a sense of pressure or weight on the head, tightness in the head, numbness or muzziness. The intensity of the pain is usually more severe in the headache of organic disease, but the patient with psychological disorder may describe his headache as agonizing.

(3) *The distribution of the headache.*—Pain with a local distribution suggests an organic cause. The converse, however, is not true. The headache of psychological disorder has a wide distribution, but this may be equally true of migraine and the headaches of arterial hypertension or cerebral tumour, and is generally true of toxi-infective headaches, and of reflex headache from visceral distension. The distribution of headache taken together with the other evidence is often important: for example, suboccipital headache occurring in the early morning and associated with vomiting is strong warrant for the suspicion of a subtentorial tumour.

(4) *The provoking and aggravating causes of headache.*—Headache due to distension of intracranial or extracranial vessels, for example, migraine, febrile headache and the headache of arterial hypertension, and the headache of intracranial expanding lesions, is often aggravated by physical effort, coughing, jolting or stooping. The headache of psychological disorder, on the other hand, is more likely to be increased by emotional stress or mental fatigue. Headache constantly provoked by coughing or straining at stool always has an organic basis, often a cerebral tumour. Constant provocation by worry naturally suggests a basis of anxiety.

(5) *The symptoms associated with headache.*—Vomiting is associated especially with migraine and the headache of cerebral tumour or other expanding intracranial lesions. The occurrence of epileptic attacks or drowsiness will naturally excite the suspicion of an expanding lesion. Most important are the symptoms associated with headache with a basis of psychological disorder. The patient whose headache has not already been classified on the basis of the previous questions should therefore always be asked how he is feeling and how he is sleeping, with special inquiry for symptoms of depression and insomnia, difficulty in concentration or abnormal fatigability. Many patients with mild states of depression or anxiety present with the leading complaint of headache.

These questions should be followed up by the ordinary plan of case-taking, in which the family history will be inquired into with particular reference to migraine or nervous breakdown, and the previous history searched for evidence of relevant information, especially head injury or infection of ear or sinuses. The examination must include inspection of the fundi and measurement of blood pressure and, not least important, an appreciation of the patient, his mood, and special preoccupations.

DIAGNOSIS

In most cases this method of examination will reveal the basis of headache at the first interview. The most common mistake made in differential diagnosis is to ascribe the headache of psychological disorder to an organic cause. Refractive errors are needlessly re-checked, unnecessary operations performed on nose and accessory sinuses, and teeth extracted wholesale, all to no avail, in hundreds of patients with headache of the "functional"

type, simply because the practitioner has never followed the lines of inquiry indicated above. The time setting, character and distribution of the headache, and above all the associated symptoms of psychological disorder, are usually evident, but the right questions have never been asked.

PROGNOSIS

This does not lend itself to discussion for it depends naturally upon the cause of the headache. A word or two may be said, however, about the prognosis in some of the common headaches. The sufferer from migraine can be assured that after the age of fifty his attacks will almost certainly decline in frequency and eventually cease. If he develops arterial hypertension, however, he will have headache as one of his most troublesome symptoms. The same is likely to be true if at any time he suffers from an anxiety state. Hence the prominence of headache in involutional depressive illness occurring in a migrainous subject. The headache of affective disorder—anxiety or depression—will improve with the mood disorder. Traumatic headaches of the organic type always improve with time, and even after the most severe head injuries are seldom a cause of disability at the end of three or four months. When convalescence from head injury is associated with an anxiety state the prognosis for recovery from the headache is related to the course of the anxiety state rather than to the lapse of time from the injury.

TREATMENT

Here again a few of the common headaches will be selected for comment. In the treatment of *migraine*, the personality of the individual and the symptoms of the attack must be considered separately. Although most sufferers from migraine will say that their attacks are causeless, if there is provoking cause it is almost always psychological tension, and it is the anxious obsessional individual who is most likely to have frequent attacks. For these persons regular sedation and simple psychotherapy are valuable. They should be given phenobarbitone, $\frac{1}{2}$ a grain (32 mg.) twice or thrice daily or, if something stronger is required at first, sodium amytal, 1 grain (65 mg.) at the same intervals, and should be made to take regular week-end relaxation and proper holidays. They should be invited to discuss their current psychological difficulties. By these means the frequency of their attacks can usually be reduced.

For the attack of migraine, if it is non-disabling or of short duration, aspirin, 10 grains (0.65 g.), taken at the onset and repeated two-hourly for as long as necessary, is best. It should be taken powdered with water to minimize gastric irritation. If the headache is disabling the sufferer had better go to bed in a dark room as early as possible in the attack and try to sleep. After a sleep there is usually improvement. For severe attacks,

ergotamine tartrate by injection is of great value; it is useless, in my experience, by mouth. It must be given early in the attack, and the patient must therefore learn to use a hypodermic syringe. He must be prepared to go to bed after the injection and remain there for five or six hours, and should be ready to accept vomiting as the result of the injection, if not of the attack. A dose of 0.25 mg. should first be tried, and the injection should be intramuscular: if not effective and without toxic effects, of which cramp in the calves is the most common, the dose should be increased to 0.5 mg. A second dose of 0.25 mg. may be given after four hours if there has been no relief. By this means the duration of the disability can usually be limited to six or eight hours, which may be a great gain for some persons who are subject to prolonged attacks.

The continuous *headache of depressive states* which is sometimes the leading symptom of the illness will respond, as does the depression, to electric convulsive therapy. One should not be in a hurry to prescribe this treatment, which is not without its disadvantages and complications, but as a rough guide it may be stated that if a patient with this type of headache is unable to follow his usual occupation and does not respond to simpler methods of treatment within two or three weeks, electric convulsive therapy is indicated.

In the treatment of *traumatic headache* it is important to recognize the interaction of physical and psychological factors. In so far as the headache is localized and constantly related to physical effort and postural change it must be respected as an indication for avoiding those exercises or movements which provoke or aggravate, but there is often an element of anxiety resulting either from the cerebral injury itself or its economic, social or legal consequences, which makes it desirable to press the patient, despite the symptom, gradually back towards a more normal mode of life. The patient with traumatic headache suffers harm more often from having his headache taken too seriously than too lightly. The anxiety needs to be treated by sympathetic understanding and advice aided, if necessary, by hypnotics and sedatives. If a patient with traumatic headache does not show steady improvement within a week or two of his injury it is useless to tell him to rest until he is better. His case needs to be reviewed both in its physical and its psychiatric aspects and a programme of treatment mapped out. For this purpose it is useful to have some guide to the probable duration of disability after a head injury of known severity as measured by the duration of the post-traumatic amnesia (P.T.A.). This information is to be found in a number of papers dealing with this subject and is summarized in the chapter on "Concussion and Contusion of the Brain" in Brock's "Injuries of Skull, Brain and Spinal Cord" (3rd edition, in the press).

THE PRESENT STATUS OF THE TREATMENT OF THYROTOXICOSIS*

By WILLIAM H. BEIERWALTES, M.D.

Assistant Professor of Medicine, University of Michigan

AND CYRUS C. STURGIS, M.D.

Professor of Medicine, University of Michigan.

THE two most important medicinal agents introduced for the control of thyrotoxicosis since the condition was first recognized in medicine are radio-active iodine and the products derived from thiourea.

MODE OF ACTION OF ANTI-THYROID AGENTS

To understand the action of anti-thyroid preparations, it is necessary to discuss briefly the control of thyroid gland activity by the pituitary-thyroid axis. It is now generally accepted that the function of the thyroid gland is

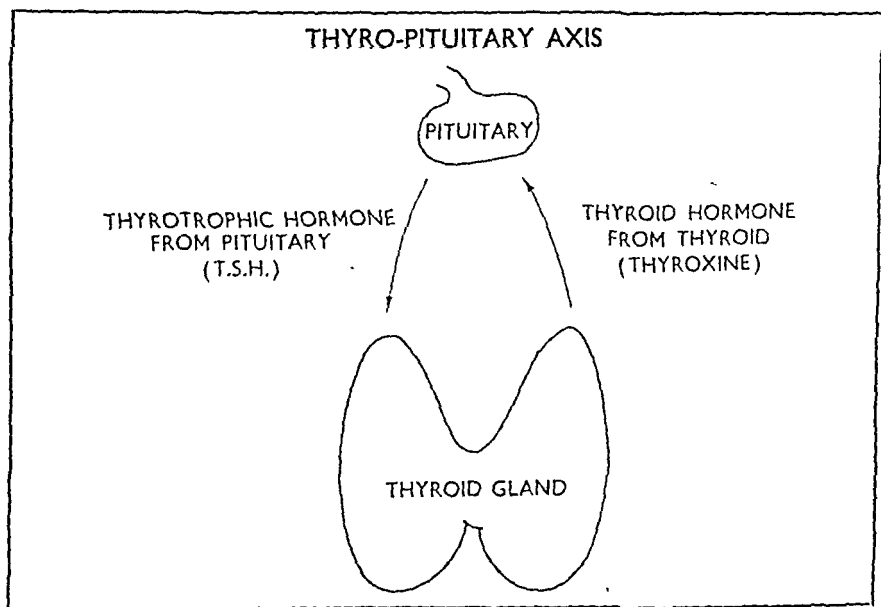


FIG. 1.—Thyroid stimulating hormone (T.S.H.—left) from anterior pituitary stimulates output of thyroid hormone (thyroxine (?), right) which in turn decreases output of T.S.H. from anterior pituitary, thus maintaining an endocrine balance between these two glands.

influenced by the stimulating effect of a hormone derived from the anterior lobe of the pituitary gland. It is known as the thyroid-stimulating hormone and is designated as the T.S.H. Reference to figure 1 will be of assistance in

*From the Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan.

clarifying its relationship. It is believed that the anterior lobe of the pituitary gland, through the T.S.H., stimulates the thyroid gland to secrete thyroxine. On the other hand, the output of thyroxine has an inhibiting effect on the rate of production of T.S.H. by the anterior pituitary. Thus an inter-glandular regulatory mechanism is thought to exist whereby each of these two endocrine organs exerts a control on the hormonal output of the other. For example, when the production of thyroxine is diminished, as in myxœdema, or when an anti-thyroid drug is given, the inhibiting effect of thyroxine on the pituitary gland is lessened and an increased output of T.S.H. occurs. This amounts to a stimulating action which has two main effects: (1) an increase in the hyperplasia and vascularity of the thyroid gland; (2) in some patients, an accentuation of the exophthalmos.

THE MODE OF ACTION OF DIFFERENT ANTI-THYROID AGENTS

Propylthiouracil.—Thiourea derivatives, such as thiouracil and propylthiouracil, produce a beneficial effect in patients with thyrotoxicosis by blocking the formation of thyroxine. This is accomplished by an action which diminishes the amount of free iodine available for the purpose of uniting with tyrosine to form thyroxine. Reference to figure 2 will show that this action of propylthiouracil prevents the liberation of free iodine from the iodides of the body by depressing the peroxidase system (DeRobertis and Grasso, 1946). The function of the latter system is to liberate iodine from its combined form in the body.

POINT OF ACTION OF ANTI-THYROID DRUGS

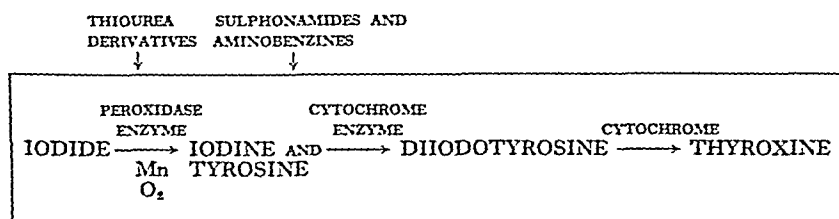


FIG. 2.—Free iodine is liberated from iodide in the presence of peroxidase, manganese and oxygen. Iodine combines immediately with tyrosine in the presence of cytochrome to form diiodotyrosine. Two molecules of diiodotyrosine are then joined in an oxygen linkage to form thyroxine. Points of action of anti-thyroid drugs are indicated above.

The effect of administering propylthiouracil or allied products to a patient with thyrotoxicosis is, then, to diminish the amount of thyroxine which is formed by the thyroid gland. When this occurs, thyroxine, which is present in the gland before the administration of the anti-thyroid drug, is released to the blood stream and is gradually utilized by the body. Eventually this supply in the gland will be exhausted, and since the thiourea derivative acts to prevent the formation of a new amount, the blood level of thyroxine must necessarily decrease and the toxic thyroid state is re-

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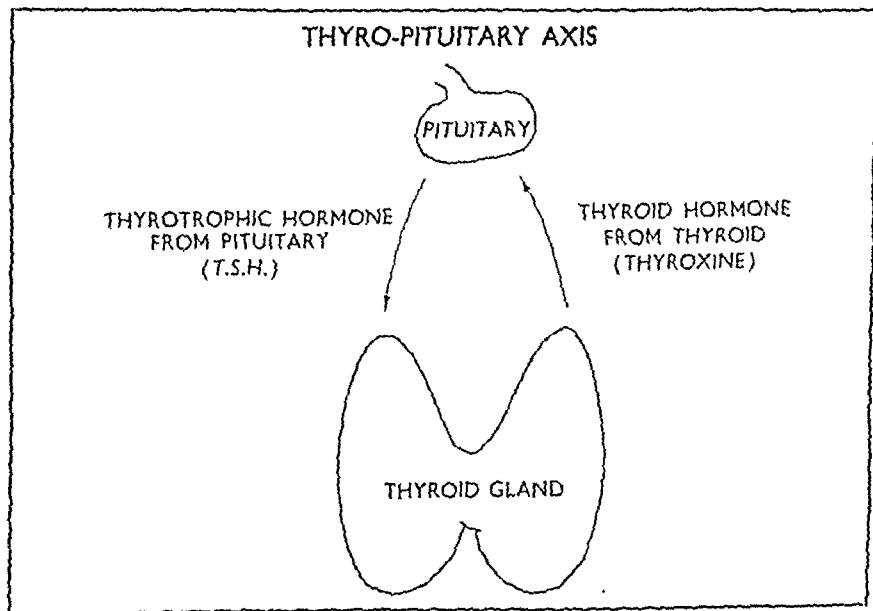


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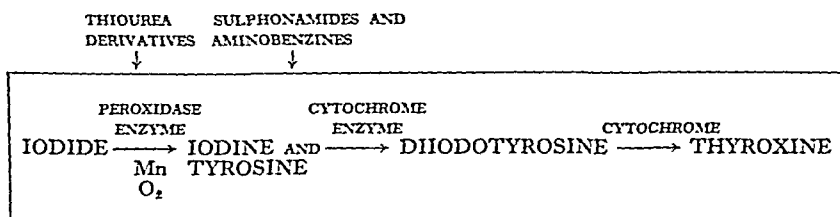


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lieved. With the fall in the level of the blood thyroxine, the inhibiting effect of the thyroid gland on the anterior pituitary is decreased, and an increased production of thyroid-stimulating hormone occurs. As previously mentioned, this results in two principal effects: (1) There is increased hyperplasia, hypertrophy and vascularity of the thyroid gland, which has all the appearances of being in a state of hyperactivity. An increased amount of thyroxine cannot, however, be produced, because free iodine is not available to form thyroxine. (2) With increased production of T.S.H., exophthalmos may become more prominent.

Aminobenzines (para-aminobenzoic acid) and aniline dye derivatives (sulphadiazine) have a similar but less effective and practical therapeutic

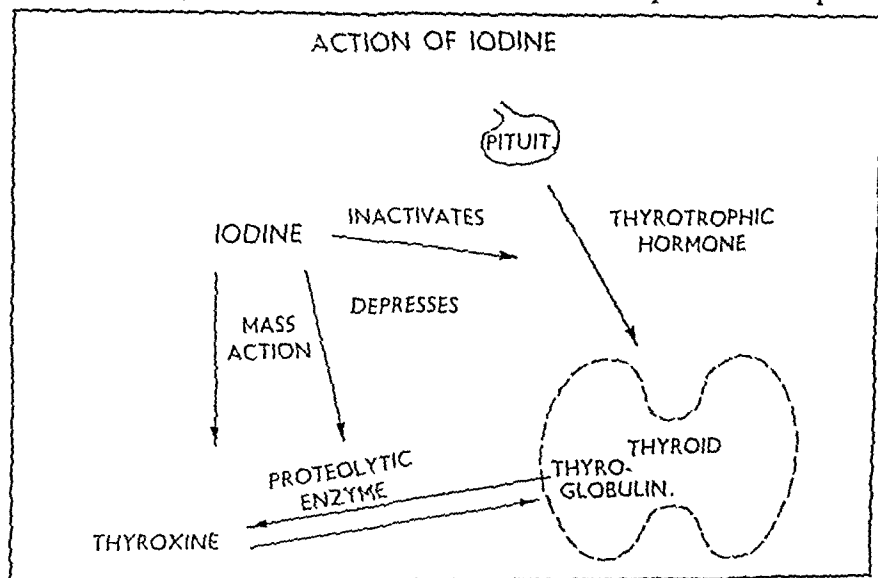


FIG. 3.—The three principal actions of iodine are: (1) inactivation of thyrotrophic hormone; (2) depression of the rate of proteolytic enzyme activity; and (3) adding one of the products of a reversible chemical reaction, thus tending to force the reaction in the direction of storage.

action to that of the thiourea derivatives. They also retard the formation of thyroxine, by making less free iodine available. This, however, is accomplished by competing with tyrosine for free iodine (DeRobertis and Grasso, 1946) after it has been liberated from iodide.

The action of iodine.—The mode of action of iodine in toxic thyroid diseases has not been clarified until recent years, although it has been employed in various preparations for many decades. It is now thought to have three important actions (fig. 3): (1) It apparently has the capacity to inactivate the T.S.H. and thereby to diminish the stimulating effect of the anterior pituitary gland on the thyroid cells (Rawson and McArthur, 1947). (2) A second action is thought to occur in the following manner: thyroxine is stored in the colloid of the thyroid gland in the form of thyroglobulin which has a large molecule with a molecular weight of 700,000 (Heidelberger

and Pederson, 1935). As such it cannot be released into the blood stream until it is acted upon by a *proteolytic enzyme* which liberates thyroxine (DeRobertis and Nowinski, 1946). This substance is in the form of a much smaller molecule, having a molecular weight of 69,000. The second action of iodine is thought to be inactivation of the enzyme which breaks down the thyroglobulin to thyroxine and permits the latter to escape into the blood stream. When this latter action cannot occur, then the thyroglobulin remains in the inactive state in the thyroid gland and is not available to exert its metabolic effect in the body (Heidelberger and Pederson, 1935). A third action, following the law of mass action (Salter and Pearson, 1936), has been demonstrated and need not here be discussed further, except to say that it tends also to decrease the amount of thyroxine in the blood.

THE USE OF PROPYLTHIOURACIL IN THE TREATMENT OF THYROTOTOXICOSIS

Experience during the past few years has shown that propylthiouracil is the most satisfactory anti-thyroid drug to employ, although it is possible that it

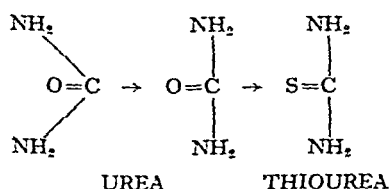


FIG. 4.—Formation of thiourea from urea. The oxygen atom attached to carbon is replaced by a sulphur atom (S) to form the carbonsulphur or "thio" group.

may be supplanted by some other closely related preparation. This drug, however, is relatively non-toxic, effective, easily administered and productive of good results in almost all patients with thyrotoxicosis. Figures 4 and 5 indicate the chemical derivation of propylthiouracil from urea. In figure 5 the dotted line encircles the thiocarbamide group on the left, which is considered essential for activity. The sixth carbon atom of the

nucleus is one of importance because this is the site of substitutions affecting the activity of all thiouracil derivatives (Williams and Kay, 1947). Figure 6 shows the first ten of these newer drugs, as listed by Williams (1947) in order of decreasing effectiveness.

Activity of propylthiouracil.—It is recognized that propylthiouracil is more effective gramme for gramme than thiouracil. The earlier observations indicated that 0.15 g. of propylthiouracil would produce the same results as 0.6 g. of thiouracil. This would suggest that the former is four times more active than the latter. Subsequent clinical observations, however, have convinced us that the optimum dose of propylthiouracil is 0.3 g., given in doses of 100 mg., three times daily, before meals. Since there is no proof that the drug is more toxic when given in such an increased dosage, we, and many others, are employing this total daily dose of 0.3 g.

The desirability of using Lugol's solution in combination with propylthiouracil.—Experience has convinced us that iodine, in the form of Lugol's

solution, should be administered routinely to all patients with thyrotoxicosis who are receiving propylthiouracil or any other thiourea derivative. The

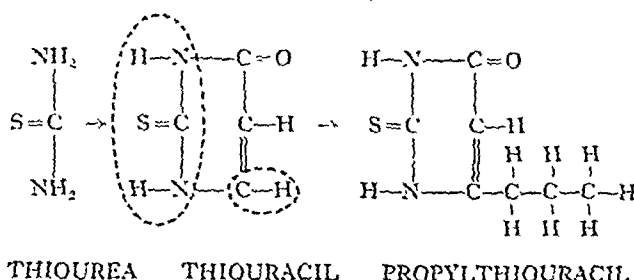


FIG. 5.—Derivation of propylthiouracil from thiourea. A right half of the compound is added to thiourea to produce thiouracil. The thiocarbamide (dotted oval left) group is a potent source of anti-thyroid activity. Dotted oval to right encircles sixth carbon atom, at which point substitutions are made to produce different compounds, e.g. propylthiouracil, methylthiouracil.

reasons for this are as follows: (1) When thiourea derivatives are given alone, although the actual amount of thyroxine formed in the body is lessened and

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| 3. 6-BUTYLTHIOURACIL | |
| 4. 6-METHYLTHIOURACIL | |
| 5. THIOURACIL | |
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FIG. 6.—Names of anti-thyroid compounds are listed in order of decreasing effectiveness, to left. (After Williams, 1947.)

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Specific details of therapy.—In preparing patients for surgery or in attempting to effect a "cure" in patients with thyrotoxicosis, 100 mg. of propylthiouracil should be given three times daily, before meals, simultaneously with 4 drops of Lugol's solution daily. This programme should be continued until a basal metabolic rate of zero is reached, and the main manifestations of thyrotoxicosis are controlled as judged by the subjective and objective symptoms. With this treatment, the basal metabolic rate declines at the average rate of about 1 per cent. per two days. Subtotal thyroidectomy should then be performed without change of dosage of either drug. No specific anti-thyroid medication need be given postoperatively.

The preoperative preparation with propylthiouracil and iodine rather than iodine alone is superior in several respects: (1) This form of medication is equally effective in patients with either exophthalmic goitre or toxic adenoma, and, in our experience, in patients with the latter condition, iodine is less efficient; (2) the basal metabolic rate is reduced entirely to normal, or even below normal, with propylthiouracil, whereas when iodine alone is used, the basal metabolic rate may be reduced, but often it does not fall lower than +20 or +15 per cent.; (3) when iodine alone is used as a preoperative medication there is a preliminary fall in the basal metabolic rate followed by an increase which may become apparent in several weeks or longer. The reduction which follows the use of propylthiouracil may be continued for an indefinite period, thereby permitting the patient to gain body weight, in case there has been excessive loss, and thus delivering the patient to the surgeon for operation in the best possible condition.

THE POSSIBILITY OF A "CURE" FOLLOWING THE USE OF PROPYLTHIOURACIL AND IODINE ALONE

If surgery is not employed, the basal metabolic rate should be allowed to decrease to about -10, at which time the propylthiouracil dosage should be reduced to 150 mg. daily, and then to 75 mg. daily if the basal metabolic rate continues to decline. The iodine dosage should continue unchanged throughout the treatment period. In general, it is advisable to administer the medication until the basal metabolic rate has been zero or less for a period of ten months. With the complete discontinuance of all anti-thyroid therapy after this time, the expectation of a "cure" is about 80 per cent. (Beierwaltes and Sturgis, 1946). Progression of exophthalmos during therapy, which is of importance only occasionally, is an indication for the simultaneous oral administration of 65 mg. of desiccated thyroid daily in order to depress the output of thyroid-stimulating hormone.

In a review of 44 patients (Beierwaltes and Sturgis, 1946), in whom an attempt was made to "cure" with propylthiouracil and iodine, the following observations were made (fig. 7): (1) Sustained improvement was more common in the exophthalmic group than in patients with toxic adenomas; (2) the "cured" patients were on the average thirteen years younger; (3) the patients in whom the best results were observed were treated on the average for two months longer, and the basal metabolic rates in these patients were normal for an average of three months longer

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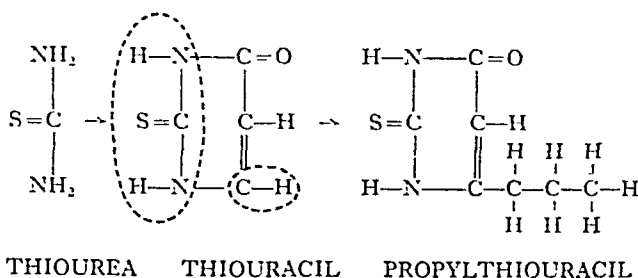


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2. 6-ISOBUTYLTHIOURACIL	
3. 6-BUTYLTHIOURACIL	
4. 6-METHYLTHIOURACIL	
5. THIOURACIL —————	$ \begin{array}{c} \text{H}-\text{N}-\text{C}=\text{O} \\ \quad \quad \\ \text{S}=\text{C} \quad \quad \text{C}-\text{H} \\ \quad \quad \\ \text{H}-\text{N}-\text{C}-\text{C}-\text{H} \end{array} $
6. ORTHO-PHENYLENETHIOUREA	
7. TETRAMETHYLTHIOUREA	
8. THIOTHYMINE	
9. AMINOTHIAZOLE	
10. PARA-AMINOBENZOIC ACID ———	$ \begin{array}{c} \text{H} \quad \quad \quad \text{O} \\ \diagdown \quad \quad \diagup \\ \text{N} \quad \quad \text{C} \\ \diagup \quad \quad \diagdown \quad \quad \diagup \\ \text{H} \quad \quad \quad \text{OH} \end{array} $

FIG. 6.—Names of anti-thyroid compounds are listed in order of decreasing effectiveness, to left. (After Williams, 1947.)

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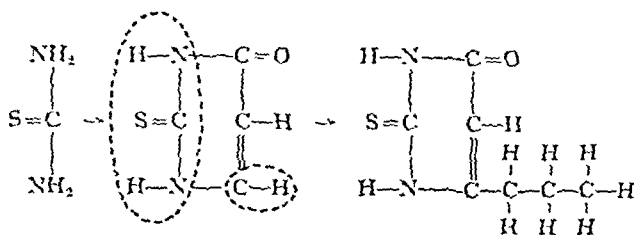
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operative administration of propylthiouracil has reduced the operative mortality in surgical clinics with a special interest in thyroid surgery, from 3 per cent. to 0.1 per cent. (Bartels, 1948). For this reason therefore any patient with thyrotoxicosis who has more than a minimally elevated basal metabolic rate, or any complication which might increase the operative morbidity or mortality, should certainly receive propylthiouracil as pre-operative medication. Furthermore, patients with exophthalmic goitre have a 75 to 80 per cent. chance of obtaining a satisfactory cure with propylthiouracil and iodine medication alone in an average period of one year, without the necessity of discontinuing work or being exposed to an operative risk (Beierwaltes and Sturgis, 1949).

TREATMENT OF TOXIC NODULAR GOITRES (TOXIC ADENOMAS)

Toxic nodular goitres, or toxic adenomas, deserve separate consideration because they differ from exophthalmic goitre in several ways. In the first place they are more readily cured by subtotal thyroidectomy, and there is less tendency to relapse following surgical treatment. Other peculiarities necessitating their surgical removal are pressure symptoms, cosmetic defects, and the possibility that they may undergo malignant degeneration. Therefore in the usual patient with toxic adenoma we consider that it is advisable to prepare him with propylthiouracil and iodine, and then do a subtotal thyroidectomy. In some cases, when there is mild toxicity and the patient is in good condition, iodine alone might be used as a preoperative preparation, but in our opinion, this is permissible in only an occasional patient.

A complete discussion of cancer of the thyroid gland will not be presented here, as the main topic under discussion is the treatment of thyrotoxicosis. It should, however, be emphasized that rarely does cancer arise in a normal thyroid gland, but usually from an adenoma. A possible exception to this is the development of a lymphosarcoma. Although the statistics indicate that cancer of the thyroid gland usually has its origin in the solitary non-toxic nodule, clinically we have observed it most commonly in a gland with multiple nodules. In addition, 26 per cent. of all cancers of the thyroid gland at the University of Michigan were removed from patients in whom thyrotoxicosis was present (Beierwaltes and Sturgis, 1949).

TOXICITY OF THIOUREA DERIVATIVES

Thiouracil should never be used, as it may cause agranulocytosis, febrile reactions, and other toxic manifestations. The development of these untoward effects following the use of this drug led to the search for an equally effective but less toxic preparation, which was responsible for the introduction of propylthiouracil. For some time this drug was thought to be without harmful effects but experience has demonstrated that this is not entirely correct. Although no fatalities have been reported following its

when the drug was omitted; (4) finally, 90 per cent. of the patients who relapsed did so within four months after treatment was discontinued.

This reaffirms the point originally made by us in 1946, and confirmed by Williams *et al.*, 1947, that if a remission persists for more than four months following complete cessation of therapy, the patient will usually continue

	Age (Average)	Per Cent. Nodular	Initial B.M.R. (Average)	Duration of treatment before dis- continuing (Average)	Duration of normal B.M.R. before dis- continuing (Average)	Duration of re- mission (Average)
Relapse 10 Patients	48	50	40%	Months 8.4	Months 4	Months 2.8
No Relapse 34 Patients	35	11.7	34%	10.6	7.3	17

FIG. 7.—The significant features of a group of ten patients treated with thiouracil who relapsed, and a group of thirty-four patients who have not relapsed after the drug was stopped, are arranged here for direct comparison. The "curable" patients are seen usually to have (1) a non-nodular goitre in a (2) young person, (3) treated for eleven months, and (4) enjoying a normal metabolism for seven months or more before the drug is stopped.

in that state for an undetermined but relatively long interval. Although many of our patients have now been in good health for from two to three years after discontinuing thiourea products, the relapsing tendency of the disorder following any form of treatment must be kept in mind when the word "cure" is used.

COMPARISON OF RESULTS ATTAINED WITH PROPYLTHIOURACIL THERAPY AND SUBTOTAL THYROIDECTOMY

Analysis of large groups of patients treated by subtotal thyroidectomy reveals that the incidence of "cure" is about 85 per cent., although in the entire group there may be certain complications such as hypothyroidism, parathyropria, laryngeal palsy, and operative deaths (VanderLaan and Swenson, 1947). The relative merits of propylthiouracil therapy on the one hand and surgery on the other, might be summarized by stating that (1) surgery cures a higher percentage of patients with thyrotoxicosis, (2) in a shorter time, (3) but with greater risk to the patient, and (4) always with the expense of hospitalization; and (5) it interferes with the patient's work for a considerable period.

From the standpoint of the highest percentage of "cures" in the shortest possible period of time, the treatment of choice in the average patient is probably the administration of Lugol's solution to a patient under sedation in a hospital, followed in a period of ten days to two weeks by a subtotal thyroidectomy. It should, however, be kept in mind that the pre-

operative administration of propylthiouracil has reduced the operative mortality in surgical clinics with a special interest in thyroid surgery, from 3 per cent. to 0.1 per cent. (Bartels, 1948). For this reason therefore any patient with thyrotoxicosis who has more than a minimally elevated basal metabolic rate, or any complication which might increase the operative morbidity or mortality, should certainly receive propylthiouracil as pre-operative medication. Furthermore, patients with exophthalmic goitre have a 75 to 80 per cent. chance of obtaining a satisfactory cure with propylthiouracil and iodine medication alone in an average period of one year, without the necessity of discontinuing work or being exposed to an operative risk (Beierwaltes and Sturgis, 1949).

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thyroid gland, especially when metastases are present, radio-active iodine may be of great value. Nevertheless, not all metastatic lesions will take up iodine, and hence the administration of this therapeutic agent would be useless. In others, the radio-active material is held by the metastatic cells as determined by the Geiger counter, and consequently subjects them to intensive irradiation.

SUMMARY

(1) The administration of iodine followed by subtotal thyroidectomy may be employed in patients with uncomplicated exophthalmic goitre who have only mild toxicity. A far more satisfactory result is attained, however, by the use of propylthiouracil plus iodine. This group also has the highest incidence of "cure" with propylthiouracil and iodine alone.

(2) The optimum preoperative treatment of patients with both nodular and non-nodular goitres of moderate to severe toxicity, is 300 mg. of propylthiouracil and 4 drops of Lugol's solution per day. This should be continued until the basal metabolic rate is at least zero.

(3) All large exophthalmic goitres and all nodular toxic goitres should be removed surgically.

(4) Propylthiouracil with iodine may be used alone in an attempt to produce a "cure" in the remaining patients, and in cases with high surgical mortality, with an 80 per cent. chance of success in a selected group.

(5) The indications for radio-active iodine are those for propylthiouracil with other limitations, such as possible danger to the patient and the difficulties of securing the material and controlling its use. Further experience with this form of therapy, under carefully controlled conditions, is necessary before it can be recommended for widespread use. The chief use of iodine to-day in treating patients with thyrotoxicosis is in augmenting the anti-thyroid effect of propylthiouracil and in reducing the hyperplastic changes produced with propylthiouracil preoperatively.

Fig. 1-5 and 7 are reproduced by courtesy of the Editor of the *Medical Clinics of North America*.

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use to date, it must be borne in mind that three cases of agranulocytosis and eleven instances of leucopenia have been reported (Bartels, 1948). Agranulocytosis and drug fever are the only two toxic reactions which are, in our experience, indications for discontinuing the drug. Although such complications are rare, the physician should, nevertheless, warn each patient who is to receive propylthiouracil, that if fever, skin rash, sore throat, enlarged lymph glands or malaise develops, the drug should be discontinued immediately, and white blood cell and differential counts should be done at once. If the patient has any of these symptoms, and a leucopenia of less than 3,500 white blood cells per c.mm., or a decrease in the neutrophils to 30 per cent. or less, then the drug should be discontinued and penicillin instituted to combat the development of sepsis. Since leucopenia is commonly observed in patients with untreated thyrotoxicosis, a complete blood count, to serve as a reference base line, should always be obtained before therapy is instituted. In the past, fatalities have usually occurred in unwarned patients who were receiving thiouracil, and in whom too much reliance was placed on white blood cell counts done at weekly or biweekly intervals to detect the early indications of agranulocytosis (Beierwaltes and Sturgis, 1946).

RADIO-ACTIVE IODINE IN THE TREATMENT OF THYROTOXICOSIS

It has been shown that radio-active iodine has a profound destructive effect on the thyroid gland in dogs and rabbits (Soley and Miller, 1948). This work also demonstrated a fact which should be kept in mind, namely, that the radio-active element also had additional effects on other parts of the body when large doses were employed. When radio-active iodine (I^{131}) with a half-life of eight days is given to a patient orally, dissolved in a glass of water, it is absorbed from the gastro-intestinal tract and taken up by the thyroid gland in the same manner as dietary iodine. The resultant necrosis and fibrosis, and ensuing loss of thyroid function, are produced by the action of the beta rays from I^{131} , which penetrate the tissue to a depth of only 1 to 3 millimetres. By such means the intensity of radiation is many times that delivered by roentgen rays, because in the latter the limiting factor is the sensitivity of the skin.

It appears certain, however, that eventually the oral administration of radio-active iodine will be a simple and effective means of destroying a sufficient portion of an overactive thyroid gland to control all evidence of thyrotoxicosis. Such treatment, when perfected, may prove to be the ultimate treatment of choice. At present, however, its use is limited by the expensive equipment necessary to the proper control of its application. Furthermore, the possibility of complications which may develop, even after a long interval, have not been evaluated. Some of these are irradiation nephrosis, parathyroprivia, irradiation of the foetus and ovaries, and pulmonary fibrosis and carcinoma. We have limited its use to patients who cannot be treated by surgery or propylthiouracil. In treating cancer of the

thyroid gland, especially when metastases are present, radio-active iodine may be of great value. Nevertheless, not all metastatic lesions will take up iodine, and hence the administration of this therapeutic agent would be useless. In others, the radio-active material is held by the metastatic cells as determined by the Geiger counter, and consequently subjects them to intensive irradiation.

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CRICKETING INJURIES

By W. E. TUCKER, M.B.E., M.B., B.CH., F.R.C.S.

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THERE are many injuries in cricket which occur with sufficient frequency to make them common to this great game, but their pathology is identical to similar injuries in other sports or those happening during the activities of normal life.

PATHOGENESIS

A direct blow on a muscle, joint or bone from a cricket ball is common, and causes some degree of contusion or bruising of the injured structure and even occasionally a fracture. Damaged cells in the area of the contusion may be so crushed and squashed that they disintegrate and are replaced by fibrous tissue. Blood and lymphatic vessels in the area of damage are also broken and there may be a considerable extravasation of blood, lymph, and serum, which may form a large hæmatoma in the proximity of the injured structure.

As the result of the blow and the subsequent pain the damaged area is often rested, and the muscles in the vicinity tend to waste from disuse atrophy, as well as from the effect of the direct injury. Thus, in the contusion of a muscle there may be damaged disintegrated muscle fibres, exudation of traumatic effusion from vessels in the vicinity and an even larger hæmatoma from torn blood vessels.

In the case of a joint there may be a capsular contusion or contusion of the articular cartilage and overlying tendons, with the formation of a large synovial effusion or hæmatoma in the vicinity. Contusion of a bone may give rise to a large subperiosteal hæmatoma or extravasation of blood in the surrounding tissues.

MUSCULAR STRAIN

Muscles overused or worked in unaccustomed exercise of a strenuous nature can produce a condition of tenderness in the muscle itself, often diffuse, but sometimes concentrated at the site of origin and insertion. This tenderness is produced by chemical changes in the muscle and may be the result of accumulation of metabolites produced by muscle action.

A muscle strain may be the result of one action of too strenuous a type, so that muscle fibres are overstretched. Often though, it is the effect of improper use of the muscles in posture and from certain occupations. Whether the strain is produced acutely, or over a prolonged period, the result is a condition of muscle tenderness and muscle atonia. As the venous and lymphatic circulation returning blood and lymph towards the heart depends entirely upon the state of the peripheral muscle tone, in the condition of muscle strain there is a tendency to a stagnation of tissue fluids in the affected area, causing further tenderness of the tissues, and even swelling.

There is little difference in the physical signs and symptoms making themselves apparent in an overused muscle or in one strained by one action or by prolonged postural and occupational strain. If a strain on a muscle is prolonged and recurrent, or that muscle is not contracting properly to withstand the strain put upon it, eventually the strain is thrown on to the joint controlled by that muscle, so that at first the ligaments are strained, and later the joint structures will show the signs and symptoms of wear and tear typical of the onset of osteoarthritis. The muscles associated with an osteoarthritic joint tend themselves to waste and become atonic, and therefore are more liable to strain with the production of muscle tenderness, so that a vicious circle may be set up between muscle strain and osteoarthritis, and this and further muscle strain.

In internal derangements of joints, as may occur in a torn meniscus of the knee, or a prolapse of an intervertebral disc, the surrounding muscles go into an acute spasm and hold the joint rigid and fixed, so as to prevent painful movement. As the spasm of the muscles passes off, either with the reduction of the internal derangement or the subsidence of the traumatic arthritic state of the joint, the muscles in spasm become tender and nodular, and the tenderness seems to spread nearer and nearer to the origin or insertion of the muscles as time elapses. Thus a muscle may be tender from:—

- (1) Overuse or unaccustomed strenuous exercise.
- (2) Sudden strain.
- (3) Postural and occupational strain.
- (4) Strain of the muscles associated with osteoarthritis of associated joints.
- (5) After-effects of muscle spasm resulting from the internal derangement of the associated joint.

The tenderness may be diffuse, or nodular and localized at certain stages, and is probably due to chemical changes occurring in the muscles. Thus it is suggested that this state of the muscles is primary fibrositis and is the result of primary muscle strain, or muscle spasm from an internal derangement of a joint or arthritis of that joint, and has not a cellular pathology as was suggested by Stockman (1920).

In certain cases the strain on a muscle may be so acute that a tear or even rupture of a muscle or tendon takes place. Usually, if this occurs, there is a larger extravasation of blood, lymph, and serum into the tissues. Rupture of certain muscles or tendons, such as the tendo Achilles, are best treated by immediate suture and this rule applies generally to those of the lower extremities where weight bearing is essential, as compensatory hypertrophy of the other neighbouring muscles cannot take place sufficiently to allow a cricketer to continue to carry out vigorous exercises as previously.

TREATMENT

In the treatment of any injury the following problems must be considered:—

- (1) The injured structure must be allowed to heal firmly, therefore there must be *rest from strain*.

(2) If there is a large synovial effusion or large hæmatoma formation at the site of injury, withdrawal by means of *aspiration or expression* through a small incision must be considered. Usually both can be performed under local anæsthesia without undue inconvenience to the patient, but naturally the procedure must be carried out *with strict asepsis*.

(3) The muscles of the injured part or the injured muscle must not be allowed to waste or form adhesions, therefore active movement of the muscles must start at once.

Jackson (1945) has shown that unless a denervated muscle is contracted at least 90 times a day it tends to waste. In muscle activity there are two types of contraction—*isotonic* and *isometric*. In *isometric* movements the muscle fibres contract and shorten, but do not lengthen, and the relation of the bony origin and insertion of the muscle does not alter. This type of contraction is observed in muscle movement in plaster of Paris. Therefore in injuries of all types absolute rest is not usually indicated. The patient should be instructed in the minutest details of what is called *active rest*:—

(1) Rest from strain. Support of all types, even plaster of Paris; refrain from weight bearing.

(2) Evacuation of large effusions by aspiration or expression.

(3) Methods to help absorption of traumatic effusion if aspiration or expression is not thought necessary.

(a) Elevation of limb.

(b) Contrast baths.

(c) Kaolin or antiphlogistine, or lead and opium, or solution of hamamelidis compresses at night.

(d) Certain active movements without strain, or in the case of a fracture in plaster, *isometric* contractions. This forces the effusion into areas where the lymphatic and vascular circulation is not damaged, and allows for rapid absorption.

(e) Certain physiotherapeutic methods: heat, massage, wax baths, anodal galvanism and short-wave diathermy.

(4) Methods to prevent muscle wasting:—

(a) Gentle non-straining active movements.

(b) Faradic stimulation of the muscles.

(c) In certain cases of nerve involvement, interrupted galvanic stimulation.

Naturally, as healing takes place, more and more strain can be thrown on the injured structure, but careful instructions must be given at each stage and the exercises graded until return to vigorous exercise is accomplished. It will be found also that adhesions in a joint or in muscles are not so likely to occur and the muscles will retain their normal extensibility.

TRAINING

Cricket, just like other sports, requires a period of training, especially if the player has to partake in the stresses and strains of three-day County matches throughout the season. After the war, many County cricketers coming back to the game seven years older tended to strain themselves more easily. This was because their tissues had lost their resilience and suppleness, partly because they had not used them regularly, and partly because tissue changes had occurred characteristic of those of a man of forty compared with those of one of thirty.

The boy and the young man should start training for the season at the beginning of April, with running, skipping and increasing periods of practice at the nets. Throwing practice should be carefully graduated, otherwise strains of the supraspinatus tendon are liable to occur. The middle-aged cricketer should be even more careful in graduating himself in the strains required for the game. We have seen that muscle strain from faulty posture or occupation can produce muscle tenderness, and it would appear from experience that often this condition of muscle tenderness precedes a definite tear of a muscle or an arthritis of a joint.

The cricketer should also be conversant with the benefit accruing from *good posture*. Prolonged standing in the field is liable to give rise to foot strain and low back strain, both of which can be prevented by foot exercises designed to strengthen the invertors and adductors of the feet, and pelvic tilting exercises to straighten the lumbar spine and strengthen the spinal flexors, i.e., the abdominal muscles and psoas. The feet should also be washed twice daily, dried carefully and foot powder used freely. The boots should not be laced tightly at the top, otherwise friction is produced on the tendo Achilles with a consequent painful tenosynovitis.

After exercise, great care should be taken to rub down or change at once, otherwise changes in the tissues occur as the result of chilling, and it is found that subsequently muscles tend to strain or tear more easily.

CONTUSIONS OF MUSCLES, JOINTS AND BONES

Treatment by the practitioner

(1) Aspiration, or expression by incision if there is a large effusion or hæmatoma.

(2) Gentle manipulative movements.

Advice to cricketer

(1) Rest from excessive walking or use.

(2) Graduated exercises.

(3) Contrast baths.

(4) Compresses: kaolin, antiphlogistine, lead and opium, at night.

(5) Support of the part.

Advice to the physiotherapist.—Heat, massage, anodal galvanism or short-wave diathermy and faradism.

Contusions or sprains of the digital interphalangeal joints are common in wicketkeepers. Skiagrams should exclude a fracture, but often these cases lead to weeks of disability.

It has been possible for a first-class cricketer to continue playing regularly, after one week's treatment, with a severe sprain and contusion of the interphalangeal joint of the left thumb in which there was a small crack in the base of the distal phalanx without displacement. This was accomplished by: (1) Resting and protecting the part with felt and crêpe bandage. (2) Contrast baths three times daily. (3) Gentle active movements with support, and in the contrast baths. (4) Anodal galvanism and gentle faradism. After three days the swelling had practically absorbed and the joint, padded with felt, was then put in a small plaster of Paris cast. On

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Naturally, as healing takes place, more and more strain can be thrown on the injured structure, but careful instructions must be given at each stage and the exercises graded until return to vigorous exercise is accomplished. It will be found also that adhesions in a joint or in muscles are not so likely to occur and the muscles will retain their normal extensibility.

TRAINING

Cricket, just like other sports, requires a period of training, especially if the player has to partake in the stresses and strains of three-day County matches throughout the season. After the war, many County cricketers coming back to the game seven years older tended to strain themselves more easily. This was because their tissues had lost their resilience and suppleness, partly because they had not used them regularly, and partly because tissue changes had occurred characteristic of those of a man of forty compared with those of one of thirty.

combined with support, protection, contrast baths, deep friction massage, anodal galvanism and faradism.

(7) Strain of the *short muscles of the foot* associated with a painful heel. This condition occurs often in heavy fast bowlers and is most difficult to cure. It may be associated with high arched feet and a calcanean spur. Some cases are associated with gout or a septic focus, and appropriate treatment for these should be included. Most cases recover with arch supports, including a sponge rubber elevation in the heel of the support, novocain injections at weekly intervals, and deep friction massage, faradism and anodal galvanism or short-wave diathermy daily.

(8) *Biceps brachii*.—This is often strained in its groove as the result of throwing, and adhesions of the tendon to its groove form limiting external rotation. Novocain injections, followed by manipulations, physical treatment and exercises, usually cure the condition.

(9) *Strains of the rhomboids*, especially on the right side. The result of chronic strain in throwing.

JOINT INJURIES

Any joint may be subjected to strains or sprains. It is usual to differentiate:

(1) *Ligamentous injuries*, which can be supported and the patient allowed to take modified strain such as walking or lifting articles at the same time as having vigorous graduated exercises, contrast baths and physical treatment.

(2) *Sprain of the joint* itself in which there is a synovitis. There may be an associated ligamentous strain as well. Weight bearing should not be allowed until all synovitis has cleared, but active non-weight bearing exercises should be started at once, combined with contrast baths and physical treatment. Aspiration is necessary in all cases of knee sprains with large effusions.

SUMMARY

- (1) The pathology of cricket injuries is discussed.
- (2) Attention to posture and training may prevent many injuries.
- (3) Avoidance of chills and draughts after exercise by rubbing down or changing immediately is essential.
- (4) If rest is advised, in most cases it should not be complete rest, but rest from strain or weight bearing, with active non-weight bearing or non-strain exercises.
- (5) Accurate instructions should be given to the patient which he can carry out himself, and to the physiotherapist, if available.
- (6) Some common strains and sprains are described.
- (7) If recurrence of an injury takes place within a short time, an aggravating cause should be considered, e.g., a septic focus or gout.

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Jackson, S. (1945): *Brain*, 68, 300.

Stockman, R. (1920): "Rheumatism and Arthritis", Edinburgh.

removal after three days the joint appeared normal and the cricketer continued to play first-class cricket on the eighth day without discomfort, the joint being protected by a small felt pad and strapping.

Contusions of the dorsum of the hand and foot can lead to months and even years of disability, whereas immediate and vigorously applied home and physical treatment will usually produce a cure, even in the worst cases, within one month.

MUSCLE STRAINS OR TEARS

(1) *Biceps femoris*, often the short head first, followed by the long head later. If a tear be present, bruising may eventually appear at the ankle. Loss of ability to extend the knee fully with ankle dorsiflexed should be countered by appropriate exercises and gentle manipulations. Vigorously applied home and physical treatment is necessary. A bad tear should be rested from strain for three weeks, and a further three weeks should be taken to restore full tone and power in the muscle, during which time exercises starting from three weeks' rest from strain are graduated to vigorous and strenuous exercises at the end of six weeks. Often these injuries keep recurring as the part is strapped and no instructions are given. Adhesions or a weak scar form which cause recurrence. In a badly damaged muscle, return to normal strenuous use should not be expected under six weeks.

(2) *Adductor longus and magnus of thigh*, especially in fast bowlers. Loss of abduction of hip countered by appropriate exercises. Treatment as before.

(3) *Left rectus abdominis and obliques* in right-handed bowlers.

(4) *Supraspinatus tendon*, the result of throwing. Degenerative changes often occur as shown by radiological evidence of calcification in chronic cases. A typical painful arc of movement is produced between 70° and 120° in abduction. Most cases recover with active treatment, novocain injections, and gentle manipulations, but in a few cases operative removal of the calcareous plaques with the whole of the acromion process is necessary.

(5) *Gastrocnemius or plantaris*.—Occasionally the typical tear of a few fibres of either of these muscles occurs, especially in middle-aged cricketers. The patient feels as if he has been shot in the calf or hit with a stick and may fall to the ground. There may be marked swelling of the ankle region in a few days owing to the seeping of effusion to this region. Active treatment with rest from strain, combined with support, will make the patient symptom-free in ten days, otherwise symptoms may persist for weeks.

(6) *Tendo Achilles*.—Occasionally rupture takes place and the tendon must be sutured. A chronic tenosynovitis of the tendon is common and is often of the sclerosing type, so that a recurring fusiform swelling forms about $2\frac{1}{2}$ " above the tendon of insertion. Friction from the seam in the back of the boot or tight lacing of the top of the boot may be aggravating causes. Some cases may be gouty in origin and are improved by a colchicum mixture. Most cases, when chronic, respond to local novocain injections

combined with support, protection, contrast baths, deep friction massage, anodal galvanism and faradism.

(7) Strain of the *short muscles of the foot* associated with a painful heel. This condition occurs often in heavy fast bowlers and is most difficult to cure. It may be associated with high arched feet and a calcanean spur. Some cases are associated with gout or a septic focus, and appropriate treatment for these should be included. Most cases recover with arch supports, including a sponge rubber elevation in the heel of the support, novocain injections at weekly intervals, and deep friction massage, faradism and anodal galvanism or short-wave diathermy daily.

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EARLY RECOGNITION OF CANCER OF THE RECTUM

By STANLEY O. AYLETT, M.B.E., M.B., B.Sc., F.R.C.S.

Surgeon, Metropolitan Hospital; Assistant Surgeon, Gordon Hospital for Diseases of the Rectum and Colon.

It might be thought that because of its anatomical position cancer of the rectum would be diagnosed at an early stage: the constant trauma of faecal matter passing over the surface of the growth and the venous congestion resulting from its presence should be sufficient reasons for producing a series of symptoms which would bring the patient to his medical practitioner rapidly, and through him to the surgeon. Such, unfortunately, is not the case.

Of a series of cases recently investigated by me, in only 9 specimens (8.4 per cent.) out of a total of 107 removed from patients upon whom a radical excision of the rectum was carried out, were the neoplasms graded pathologically into type A (those carcinomas in which there was no spread of the disease outside the rectal wall). In 46 specimens (43 per cent.) the growth had spread outside the rectal wall but the lymph nodes were still free of cancer, and in 52 (48.6 per cent.) there was involvement of the lymph nodes at the time of operation (type C case). This series does not include those cases deemed inoperable, so that the number of patients in whom diagnosis had been established at an early date in the progress of the cancer was even less than the low figure of 8.4 per cent.

The importance of early diagnosis in this as in all types of cancer is made clear by a five year follow-up of these cases. Of those surviving the operation, all the patients in the series in whom the growth was classified as of type A were alive and well at the end of this period, whereas in type B growths only 56.6 per cent. were alive and disease-free, and in type C growths the survival rate had fallen to 28 per cent. (table 1).

TABLE I

FOLLOW UP OF 76 CASES SUBJECTED TO ABDOMINO-PERINEAL EXCISION OF RECTUM

Classification of growth	No. of Patients	Alive and well at			Died free of growth before 5 years	Died of cancer	Un-traced	Percentage 5 years survival
		5 years	5-10 years	Over 10 years				
A	6	5	3	3	1	0	0	100
B	30	17	12	7	1	12	0	56.6
C	40	11	10	4	0	28	1	28

Although the vast majority of patients are sent to the surgeon at a comparatively late stage in the disease, most neoplasms of the rectum have given

rise to symptoms months previously. Amongst a series discussed below the average time between the initial symptom noticed by the patient and the date of admission to hospital was nine months. These initial symptoms, however, often pass unheeded by the sufferer, and even when they are reported to the doctor they are sometimes not recognized as those of early rectal cancer.

It is the main purpose of this article to draw attention to these early symptoms, and to suggest how they may be correlated with the physical signs so as to facilitate early diagnosis. The clinical picture of a patient suffering from profuse diarrhœa, anæmia, gross loss of weight and general cachexia must be forgotten as typifying the patient with cancer of the rectum. In its place must be the picture of a fit man or woman complaining of one or more of the early symptoms to be discussed subsequently.

Age and sex incidence.—Although the disease has been described in those under the age of twenty as well as in octogenarians, the great majority of cases occur in those between the ages of forty-five and seventy. Males are affected more commonly than females, the ratio being about 2.5:1.

EARLY SYMPTOMS

Disturbance of normal bowel routine.—The symptom first noticed by each of 155 patients is recorded in table 2. It will be seen from this that some form of disturbance of normal bowel action was the most common presenting symptom, having been observed by 69 (44.5 per cent.) of the total. This disturbance is often not dramatic. The patient may have noticed that he has had to take purgatives recently, perhaps for the first time in his life as a regular habit. He may complain that he has to strain more to get his bowels

TABLE 2
INITIAL SYMPTOMS NOTICED BY 155 PATIENTS

Initial symptom	Number of Patients	Approx. percentage of total number
Diarrhœa	43	28
Increasing constipation	18	11
Alternating diarrhœa and constipation	8	5
Bleeding on defæcation	40	26
Discharge from anus	15	10
Pain in rectal and perineal regions	15	10
Lump noticed at anus	4	2
Backache	5	8
Loss of weight	2	
Low abdominal pain	3	
Increasing flatulence	1	
Pain down left leg	1	

open, and at the end of such act the feeling of completeness of defæcation is absent. Other patients may complain of attacks of diarrhœa, often fleeting

in nature, but recurring, whereas sometimes the patient may give a history of constipation alternating with the diarrhœa.

Whatever the disturbance of bowel action complained of by a patient in the cancer age-group, or elucidated on questioning, such patient should be regarded as under suspicion of suffering from rectal carcinoma until complete examination has excluded this possibility.

The symptoms of bowel dysfunction are readily explained pathologically. Although the ampulla of the rectum, in which the majority of the growths occur, is large, the presence of an ulcerating neoplasm in the bowel wall gives rise to spasm of the adjacent bowel, so that even with an early and small cancer the passage is reduced. Increasing constipation results, which later, as a result of irritation of the bowel mucosa by the secretion from the surface of the growth, gives place to a pseudo-diarrhœa.

Bleeding per rectum.—In 40 patients (26 per cent.) this was the first symptom noticed, without any associated diarrhœa or constipation. Hæmaturia results in the patient rushing to the doctor, who rightly sends him at once for investigation. Bleeding per rectum, however, is not only ignored by the sufferer, who has read all about piles, but is often overlooked as a presenting symptom of cancer of the rectum by his doctor. Until the presence of such a neoplasm is disproved the patient in the cancer age-group complaining of bleeding per rectum should again be regarded as suffering from the disease until its presence is disproved. Only by adopting such an attitude to this and other early symptoms of the disease will an increasing rate of early diagnosis be achieved.

The bleeding may be as bright red as that occurring from hæmorrhoids. Indeed the bleeding may actually be from piles enlarged and accentuated by the presence of the growth in the rectal wall above, and their presence and identification does not exclude the possibility of a neoplasm at a higher level. Bright red hæmorrhage is also likely when an adenomatous polyp or a villous papilloma is enlarging into malignancy and its delicate surface is being eroded by the impaction of fæcal material upon it. It is also a symptom in those cases in which a fairly large blood vessel has been eroded on the surface of a carcinomatous ulcer. Usually, however, the bleeding consists of dark blood often mixed with fæcal matter and the mucopurulent discharge of the ulcer surface. Sometimes the bleeding is associated with the passage of fæces, and at other times the patient passes the blood without any accompanying bowel action.

Discharge from the anus.—This was the initial complaint in 15 patients (9.7 per cent.), the discharge being noticed at the time of defæcation, or the patient's attention having been drawn to it by a feeling of constant moisture in the anal region associated with soiling of the clothes.

Pain in the rectum and/or perineal regions.—This presenting symptom occurred in 15 cases (9.7 per cent.) and is associated with low rectal growths or growths in the anal canal. The symptom may amount to severe pain or

be a vague sensation of discomfort. In growths of the anal canal the pain is particularly associated with defæcation and is of the same character as the pain of fissure-in-ano. In fact the condition is sometimes mistaken for the latter and is treated as such. Because of the pain in such cases associated constipation is marked.

Appearance of a mass at the anal orifice.—This was the initial feature of the disease in 4 patients (2.6 per cent.), and in 2 of these 4 cases the condition suspected for three months, before reference to a surgeon, was that of thrombosed hæmorrhoids. The growth in such cases is usually low down in the rectum or anal canal, but on occasion a neoplasm higher up may act as the apex of an intussusception and appear at the anal orifice in this manner.

Other initial symptoms.—These are tabulated in table 2 and consist of backache, loss of weight, low abdominal pain and increasing flatulence. They are rare as presenting symptoms, but it is well to remember them in considering the diagnosis of cancer of the rectum.

EXAMINATION OF THE PATIENT

A *general examination* must of course be carried out, but usually this reveals little. In a thin patient with lax abdominal wall it is sometimes possible to identify a high rectal neoplasm by deep palpation in the pelvis, but this is uncommon. In early cases, abdominal distension is absent, and the presence of an enlarged liver with secondaries is, of course, only found in late stages of the disease.

It is the *rectal examination* that is of paramount importance in every case in which there is a vestige of suspicion that the patient may be suffering from rectal cancer. Too often this examination is overlooked.

In conformity with the teaching of the late Ernest Miles, I would emphasize that the patient be examined lying in the right lateral position with the examiner employing the left index finger. In certain cases, neoplasms not palpable with the patient lying on his left side, can be felt when the opposite position is adopted. With the left index finger in the rectum and the patient on his right side, the pelvic colon falls towards the right side, dragging the upper, somewhat mobile portion of the rectum with it. It therefore falls towards the examining finger, whereas if the patient is examined in the left position it falls away from it.

The height to which the examining finger can reach and therefore the number of cases of cancer of the rectum that can be palpated depend not only upon the length of the examining finger, but also upon the bulk of the patients' buttocks. On an average, however, between 60 and 70 per cent. of cases are readily palpable.

If no neoplasm is felt the patient should be made to sit up and strain down, the examiner's finger being retained in position. On such an examination the lower margin of a growth can sometimes be identified in those cases in which it is not palpable with the patient lying down in the lateral position.

The edges and surface of the growth are usually hard and irregular, but when dealing with an adenoma or villous papilloma that is undergoing malignant change, the neoplasm is soft and lacking the customary craginess. It is impossible in most cases, except perhaps by a consideration of their extent, to say whether such a tumour is malignant or not by palpation alone.

Biopsy, repeated if the section shows no sign of malignancy, is the only sure diagnostic method. In any case, if such tumours are found, the patient should be referred for surgical treatment, as these tumours must be considered as premalignant.

In the examination of female patients the cervix or body of the uterus may sometimes be mistaken for a rectal tumour by those not constantly practising rectal examination. The two lips of the cervix, palpable through the rectal wall, will usually identify this, and if there is any doubt a bimanual examination with fingers of the other hand in the vagina will dispose of this.

When a palpable growth is not found it is important to observe the presence or absence of two other signs. First, the presence of any ballooning of the rectum. Normally the rectal wall is in loose but close contact with the examining finger, but when a neoplasm is present at a higher level the innervation of the lower rectum is interfered with and it may become atonic and ballooned. In such cases the finger feels lost in a large cavity in which it may be freely moved without coming into contact with the rectal wall.

Secondly, on withdrawing the finger, the stall or glove must be closely examined for the presence of blood or blood-contaminated discharge. Unless there are obvious hæmorrhoids with no other signs of disease such a finding indicates that further investigation is necessary. It is highly suggestive of a high rectal carcinoma.

Proctoscopy is not necessary. All that can be seen within its limited field can be visualized by tactile inspection. If doubt remains at the end of the examination and the history is suggestive of carcinoma, the patient must be referred for *sigmoidoscopy*. This can be carried out in the out-patient department with little discomfort to the patient, and it will finally confirm or exclude the diagnosis. A *barium enema* will not show a filling defect in every case of rectal cancer, and even with a negative result sigmoidoscopy must still be performed.

DIFFERENTIAL DIAGNOSIS

A number of diseases may simulate certain features of the history and findings of carcinoma of the rectum, and the important differential diagnoses of hæmorrhoids and fissure-in-ano have been emphasized.

Ulcerative colitis presents many similar diagnostic points, although the disease usually affects younger people, and if seen for the first time amongst those of the cancer age there is generally a past history. In addition, patients with ulcerative colitis are ill patients compared with those suffering from early rectal cancer: with fever, anæmia and toxæmia. *Sigmoidoscopy*, however, is always an essential diagnostic step.

Diverticulitis of the lower pelvic colon may also cause confusion in diagnosis: with its symptoms of disturbance of bowel function and abdominal pain, and with the presence of small masses sometimes palpable

through the rectal wall it simulates carcinoma of the upper rectum. Indeed, carcinoma may arise in association with such a condition. For differentiation, most cases require full investigation.

Chronic amœbic infection of the colon, far more common since the war, will also produce the symptoms of diarrhœa and rectal discharge. Again sigmoidoscopy is necessary, and scrapings from the ulcers will often reveal the presence of the amœba. Occasionally in this disease a granuloma may form in the rectum indistinguishable from rectal cancer except by biopsy.

Multiple polyposis of the colon gives a clinical picture suggesting carcinoma. Rectal examination may reveal polypi in the rectum. This disease is of pre-malignant nature and requires colectomy and diathermy of the rectal polypi for its cure.

Single *adenomas*, or *villous papillomas*, giving rise to bleeding and discharge, must also be treated surgically on account of their known tendency to undergo malignant change. Rare *granulomas*, such as those due to actinomycosis, bilharzial infection or lymphopathia venereum may simulate a rectal cancer, and will also require biopsy for differential diagnosis.

Finally, *sarcoma* or *malignant melanoma* of the rectum are found, but their differentiation from carcinoma is recognizable only on biopsy, and in any event their treatment is the same as for this condition.

CONCLUSION

This article has been a plea for earlier diagnosis. In early cases the follow-up results following radical excision of the rectum are good, and the patient stands an excellent chance of being cured. As many as 5,500 men and women die annually from this disease in England and Wales. Some of them would be saved if, at the time they report their symptoms, the question of cancer is uppermost in the practitioner's mind. In addition, suitable public propaganda is required along the lines now being considered by the British Empire Cancer Campaign, in order to impress upon the public the necessity and advantages of seeking medical advice at as early a stage as possible.

PENICILLIN BY THE SUBCUTANEOUS ROUTE

By DAVID WHEATLEY, M.B., B.CHIR.

THE exigencies of general practice often stimulate the adoption of methods which would seem, from existing facts, to be far from ideal. The advent of penicillin has, in many cases, presented such a problem, and a compromise solution is widely used both in general practice and in the hospital out-patient department (Barclay, 1949). This consists of substituting the more convenient twice-daily injections for the accepted three-hourly administration. To overcome the decline in penicillin blood level over such a period, doses of the order of 100,000 to 200,000 units are administered in the hope that a sufficiently active penicillin blood level will still remain at the end of each twelve-hourly period. In practice, the results are sufficiently good to justify the procedure. It would seem, however, to be an unscientific compromise to an accepted method.

Why is this method successful? It can possibly be explained by the selective action of penicillin on actively dividing organisms, as has been demonstrated by Chain and Duthie (1945) during *in vitro* experiments. An interval without penicillin in the blood may allow dormant bacteria to undergo active multiplication, thereby rendering themselves susceptible to the next dose of the drug. The use of a fairly large dose might be necessary to ensure the destruction of all the actively dividing organisms present at the time of the injection. On this hypothesis, an interval of twenty-four hours would not appear to have any disadvantage over one of twelve hours, and would be of greater convenience.

Hoffman (1946) showed that penicillin blood levels are maintained in exactly the same manner after subcutaneous as after intramuscular injection. He concludes that the former is the mode of administration of choice. Crystalline penicillin, being free of impurities, should not give rise to pain or local reaction when injected subcutaneously. I shall endeavour in this short article to show that this is the fact, and to demonstrate clinical results sufficiently satisfactory to justify its use.

RESULTS

In the majority of cases a standard dose of 200,000 units, dissolved in 1 ml. of sterile water, was employed. This injection was given subcutaneously, at 24-hour intervals. For children under five years, the dose was halved.

Minor pyogenic conditions (43 cases).—Only cases with some definite indication, such as pyrexia, adenitis, lymphangitis or marked local reaction, were treated with penicillin. Similarly, in order to avoid misinterpretation

of results due to spontaneous recovery, only those seen within a few days of onset are recorded (table 1).

TABLE 1

Lesion	No. of cases	Av. no. of injections	Av. no. of days for scar formation	Remarks
Superficial whitlows ..	10	4	6	1 incised
Palmar space infection	1	4	12	Incision necessary
Carbuncles	5	4	9	—
Boils	13	4	5	—
Styes	6	2-3	3-4	—
Infected cuts ..	7	4	8	—
Alveolar abscess ..	1	2	3	—

Acute otitis media (7 cases).—All these patients were seen early in the infection, and the aim was to prevent either perforation of the drum, or the necessity for paracentesis. In the first five cases sulphonamides were also administered, in full doses, and no conclusions can be drawn from these results (table 2).

TABLE 2

No. of cases	Av. no. of injections	Av. no. of days for drum to return to normal	Remarks
7	2-3	3	No perforation or other complication in any case

Pneumonia (3 cases).—Owing to the serious nature of this disease, full courses of sulphonamides were also administered, and no conclusions are drawn from the results. The average number of injections was seven, and the average number of days for resolution was nine. Of two patients who recovered, one had lobar and the other broncho-pneumonia. The latter was a baby of six months. The other patient, who died, was a man of sixty-two, with a deformed spine and many years' history of chronic bronchitis and asthma. He had been given oral penicillin on a previous occasion, and it is possible that the invading organisms had thereby acquired resistance to penicillin.

Miscellaneous (2 cases).—One case of puerperal mastitis, and one of acute tonsillitis. In each case four injections of penicillin were given, and the symptoms subsided in four days.

VARIATIONS IN DOSAGE

A few cases were studied using different dosage schemes: eight patients were given 100,000 or 200,000 units twelve-hourly, whilst six were given 500,000 units every twenty-four hours (table 3 and 4). Little difference was observed in the results, and these series were therefore discontinued.

TABLE 3
200,000 or 100,000 units every 12 hours (8 cases)

Disease	Av. no. of injections	Av. no. of days to subside	Remarks
Acute mastitis with breast abscess ..	8	14	Incision necessary
Paronychia	3	7	Incised
Multiple boils ..	5	5	—
Infected cuts (2) ..	3-4	5-10	—
Carbuncle (2) ..	8	9	—
Lobar pneumonia ..	9	6	Sulphonamides

TABLE 4
500,000 units every 24 hours (6 cases)

Disease	Av. no. of injections	Av. no. of days to subside	Remarks
Superficial whitlow	3	6	—
Acute tonsillitis ..	2	4	—
Boil	2	4	—
Stye	2	3	—
Puerperal mastitis ..	8	No permanent cure	Inhibition of lactation with stilbæstrol necessary
Leg infection ..	4	7	—

CASE HISTORIES

The following cases are described as being typical of the results obtained in this series:—

(1) A young girl, subsequent to the squeezing of a "black-head" on her cheek, complained of a swelling there, which "continually came up and burst". On examination there was a reddened, indurated area, just below the left eye, with much swelling of that side of the face. Temperature 99° F. (37.2° C.), pulse 120. In view of the potential risk of cavernous sinus thrombosis, penicillin was given: 200,000 units of the crystalline product, subcutaneously, at 24-hour intervals. After the first twenty-four hours, temperature and pulse rate were normal and the mass was fluctuant. By the fourth day it was discharging freely, and subsequent healing was rapid, with no recurrence.

(2) A five-year old boy complained of earache of three days' duration. Temperature was 102° F. (38.9° C.), and the pulse rate increased proportionately. The left ear drum was inflamed and bulging. 200,000 units of crystalline penicillin in 1 ml. of sterile water, were injected subcutaneously. Twenty-four hours later the pain was much better, the temperature normal, and the condition of the drum subsiding. Two further injections were given at 24-hour intervals; on the third day all signs and symptoms had disappeared.

(3) A middle-aged workman suffered a traumatic laceration to his right foot. He was seen two weeks later with an infected and swollen foot, severe inguinal adenitis and a temperature of 100.2° F. (37.9° C.). The pulse rate was normal. He was given 500,000 units of crystalline penicillin in 1 ml. of sterile water, subcutaneously. Twenty-four hours later the temperature was normal and the foot much better. Injections were continued at 24-hour intervals for four days. By the seventh day the condition had completely subsided, and the purulent area was healed.

(4) A girl of six and a half years was taken ill suddenly with vomiting and a high temperature. Examination revealed only epigastric tenderness. During the ensuing twenty-four hours, vomiting was repeated several times, the temperature reached 104.4° F. (40.2° C.), and the patient became delirious. There was now slight pain in the lower left chest, and an increased respiration rate. Lobar pneumonia was diagnosed, although there were still no signs in the chest. Crystalline penicillin, 100,000 units in 1 ml. of sterile water, was given subcutaneously, and treatment with sulphadiazine instituted (1 g., followed by 0.5 g. four-hourly). A second penicillin injection of 100,000 units was given nine hours after the first; and eighteen hours after the first injection, the temperature was below normal and the patient appeared to be almost well. Further similar penicillin injections were continued twice daily for three days, and a well-marked consolidation of the left lower lobe appeared on the second day. Thereafter, single daily doses of 100,000 units were given until resolution occurred on the sixth day. The full course of sulphadiazine was administered.

CONCLUSIONS

No pain or discomfort as a result of the subcutaneous injection of crystalline penicillin was experienced in any of the recorded cases. Results of treatment could only be assessed in terms of success or failure; and no comparisons can be drawn with other methods of treatment. The only failures were one case of palmar-space infection, in which incision was necessary; one case of breast abscess for which incision was necessary; one case of puerperal mastitis, in which inhibition of lactation with stilbæstrol was necessary; and one case of pneumonia, which terminated fatally. These were out of a total of 69 cases.

The object of this article is to demonstrate the use of crystalline penicillin by subcutaneous injection. It is felt that it may reasonably be concluded that this method of administration has many advantages over intramuscular injections, especially in general practice, as it is a quick and easy method to use; in particular in children, as it does not give rise to the pain of intramuscular injections, or the ensuing apprehension of the subsequent injections.

I am indebted to Imperial Chemical (Pharmaceuticals) Ltd., for supplying me with crystalline penicillin G, before this product became generally available.

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CURRENT THERAPEUTICS

XVIII.—ANDROGENS

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It is probably true that the greater part of the androgens consumed have been prescribed in an attempt to alleviate psychogenic impotence, an attempt foredoomed to failure, for you cannot put more than a pint of beer into a pint pot. The failure of the male hormone in its most obvious application should not be allowed to obscure its true value, to both men and women, in a number of distressing conditions.

USES IN MALES

Testicular deficiency.—The eunuch, whose testicles have been entirely destroyed by accident, disease, surgical necessity, or religious rite, and the eunuchoid male, whose testicles have failed to develop fully owing to local disorder or pituitary deficiency, have little or no beer in their pint pots. The results of treatment by the androgens are brilliant but, judging by the number of patients who for many years go untreated, still too little known. Of the diagnosis of the eunuch no more need be said. It is the eunuchoid boy who so often goes undiagnosed, accumulating often with the passage of the years a succession of psychological traumas which time can never wholly heal. His long, narrow, hairless body, soft skin, weak muscles, and unbroken voice single him out from amongst his schoolfellows at an age when he most desires to be of the herd and fears to be egregious. Vaguely at first, and later poignantly, he realizes that he is excluded from the erotic experiences proper to youth and that the instinct of the young female animal places him unerringly in a different category, lower than his friends. Such boys, if diagnosed before the middle teens, can be saved much misery. Their physical and emotional development can be directed into normal pathways, so that they grow to manhood subject only to one handicap, their inability to breed. Diagnosed at a later age, less, but much, can still be done: their hair can be made to grow, although perhaps somewhat sparsely, their muscles to develop, their voices to break, their penes to enlarge and tumefy. But the sense of inferiority already acquired is difficult to shed and a psychogenic impotence may survive the removal of its organic cause.

The removal of diseased testicles undertaken without the wise psychological preparation of the patient, may have disastrous emotional and social results. It is important that the patient should not be made impotent even during the short term of his convalescence, and that he should know and believe before the operation is performed that his sexual powers will be unabated. This can be ensured by the implantation of testosterone at the

time of operation. The pain of an erection the day after orchidectomy is borne not only with fortitude but with jubilation, and the onset of psychogenic impotence is forestalled.

The male climacteric.—The concept of a climacteric in the male is open to grave doubt. There is in men no sudden cessation of gonadal activity similar to the female climacteric. The reduction in sexual activity is gradual and may begin as early as forty or as late as one hundred years of age. Proceeding slowly in a man of adult mind it passes unnoticed, the sexual epoch no more regretted by the old man than childhood by the young. Sometimes, however, the change is more rapid and may take unawares a man who has not yet begun to notice in other ways the passage of the years. It has been recorded that in such patients various vasomotor disturbances may be manifest, or irritability, fatigue and depression, the total syndrome somewhat resembling the female menopause. I confess I have never seen a patient whose condition tempted me to such a comparison or one in whom the symptoms were not more easily explicable by arterial degeneration or by plain boredom and dissatisfaction. Nevertheless, I consider the administration of androgens in such cases to be occasionally justifiable. The effects on the peripheral circulation may, as will be seen later, be good, and there is no doubt that in the man whose testicular function is failing, albeit physiologically, the male hormone may have a noticeably tonic effect, increasing the patient's energy and sense of well-being. It is perhaps to the good that the effect on potency is slight or absent. Sexual potency depends upon a chain of which the endocrine function of the testicles is but one link. A man is not old because his testicles are failing: they are failing because he is old.

Other suggested uses in men.—Androgens have been used in the treatment of *homosexuality* with, as might be expected, no success. In the vast majority of homosexual patients there is no evidence of testicular deficiency. One is occasionally struck by the feminine (or rather unmasculine) contours of a homosexual individual, but I have no doubt that the concurrence is fortuitous. The tragedy of the lives of most men with gonadal deficiency is indeed that they are mentally heterosexual but unable to express their bias.

In some experimental animals, testosterone maintains spermatogenesis after hypophysectomy. This fact has led to its use in *azoospermia* and *oligospermia* in men. Most men suffering from these defects show no evidence of any lack of testosterone, and I have not yet heard of a pregnancy which could with confidence be ascribed to the treatment of the husband with androgens, or indeed with any other glandular preparation.

According to Werner, the treatment of *benign enlargement of the prostate* by means of androgens was first suggested (although, I would add, never advocated) by Zuckerman and myself. It is therefore fitting that I should set down my mature views. The rationale of the treatment is clear, but a carefully controlled experiment conducted on behalf of the Medical Research Council by Band, Burrows, Carver, Dix, Walker, and myself, but

never published owing to the onset of war, showed that in practice no apparent diminution of the prostate is produced, even by a dosage as high as 200 mg. weekly of testosterone propionate. Nevertheless, in many cases the symptomatic improvement is remarkable. It is possible that this may be ascribed to suggestion or to the general "tonic" effect of androgens in elderly men to which reference has already been made. But according to Hamilton and Gilbert, the improved urinary function often found is due to increased tonus of the bladder. However this may be, it is questionable whether the treatment is justifiable, especially in view of recent improvements in the technique of prostatectomy. It is not always easy, even for an expert, to diagnose the earliest stages of prostatic cancer, and it is certain that malignant changes are accelerated by the administration of androgens.

Androgens have been used in the past in the treatment of the *undescended testicle* and there seems little doubt that the treatment is occasionally effective. It is not recommended, for far from stimulating the onset of normal testicular function, it actually depresses it. In large doses it may lead to embarrassing sexual behaviour. The chorionic gonadotrophin is preferable, for it increases the size of the testicles, is more generally successful, and does not lead to premature sexual manifestations or to any other harmful results. The androgens have been recommended in advertisements for the treatment of many other complaints in men, including anxiety neurosis, "neurasthenia", adiposity, acne (!), and ejaculatio præcox. They are valueless in all of them.

Harmful effects in males.—The only effect which can be described as harmful is the excessive sexual activity of the eunuch to whom a too high dosage is given. Even this effect is transient, and the eunuch does not mind much. Excessive sexual activity cannot be aroused in men who were not previously sexually deficient.

USES IN FEMALES

The use of the androgens in the treatment of women has been the subject of criticism on the grounds that it is dangerous and unphysiological. The criticism is inadmissible, because the so-called "male hormones" are produced, albeit in smaller quantities, in women as well as in men, the site of production being the adrenal cortex. Testosterone inhibits the vaginal cornification induced by œstrogens, suppresses the normal cyclical changes in the endometrium, and prevents the ripening of the ovarian follicle by suppressing the production of pituitary gonadotrophin.

Excessive uterine bleeding.—Menorrhagia, whatever its cause, can usually be suppressed by the administration of methyl testosterone by mouth, in a dosage of 5 to 15 mg. daily. Such doses do not usually have any virilizing effects. In the few patients who do not respond, results can be achieved by the injection of testosterone propionate, although in a few cases a dosage as high as 1 g., administered over a period of one month, may be needed. Virilization is then likely but is only transitory. Alternatively, testosterone

(50 to 200 mg.) may be implanted. Nevertheless, the ease with which bleeding may be stopped and the number of unnecessary hysterectomies in young women which can thus be obviated, must not be allowed to obscure the necessity of accurate diagnosis. Androgens should never be administered without a careful vaginal examination and, except in young girls, an endometrial biopsy. Although the risk of missing a diagnosis of malignant or inflammatory disease is negligible in the very young, and a biopsy undesirable, alternative methods of treatment, including general measures and the administration of thyroid, should have careful consideration. It is as well to remember also that menorrhagia may be the first sign of thrombocytopenic purpura and that it may be of purely psychological origin.

Fibroids.—When fibroids are associated with excessive bleeding, androgenic treatment is usually extremely effective, bleeding ceasing for a year or more after the implantation of 50 to 200 mg. of testosterone. The size of the fibroids is often diminished and pressure symptoms are partially relieved. I have not yet seen a case in which relapse did not ultimately occur. The treatment should be regarded as temporary except in mild cases nearing the climacteric in which a spontaneous regression may be hoped for.

Dysmenorrhœa.—The pathology of dysmenorrhœa is still obscure, but it appears that in some women the pain is due to an excessive sensitivity of the myometrium or the uterine vessels to the action of œstradiol. In such cases relief may often be obtained by the use of testosterone, given either by mouth as methyl testosterone, by injections of testosterone propionate, or by the implantation of pellets of testosterone itself. The disadvantage of implantation in these cases is the difficulty of determining in advance the dose which will relieve the symptoms without deranging the menstrual cycle. Oral administration of methyl testosterone, continuously in small doses, is the method of choice. When a comparatively painless menstrual period has been achieved, it is worth while trying the effect of administration during the second half of the cycle only.

Frigidity.—Lack of libido in women corresponds closely to impotence in men. It is usually psychologically determined and a full response to hormone therapy can be expected in few cases. It appears, however, that in some patients it is the result of disappointment after a repeated failure to achieve orgasm and that this failure may be due to insensitivity of the clitoris. In such cases, treatment with androgens increases the size of the clitoris and its erectile capability, thus awakening a greater interest in the act of copulation. Treatment is best administered by the gentle inunction of an androgenic ointment into the clitoris itself, general effects being thus avoided.

Pre-menstrual symptoms.—A large number of women complain of unpleasant symptoms in the last week before the beginning of each menstrual period. Some are unduly depressed or irritable, others suffer from headaches or pains in the breasts, and yet others from blocking of the nose, rhinorrhœa or asthma. Such symptoms may often be relieved by the administration of methyl testosterone by mouth during the latter half of the

cycle, the dose being adjusted to such a level that the symptoms are relieved without derangement of menstrual regularity. Before such treatment is used, the effects of dehydration should be tried. Many women are relieved by a low salt, low fluid regime combined with diuretics.

Fibro-adenosis of the breasts.—This term is now coming into use as a convenient and more accurate substitute for the old misnomer "chronic mastitis". The hypothesis at present holding the field is that many of these cases are due to an increase in the œstradiol-progesterone ratio. Testosterone has not only an "anti-œstrogenic" effect, but it also possesses some progesterone-like properties. Its success in the treatment of painful lumpy breasts is often dramatic. It can be given by inunction in an ointment base, but most women regard this method as too time-consuming. Methyl testosterone by mouth is usually the most convenient means of administration, although in severe cases implantation is worth considering.

Endometriosis.—The ectopic endometrial tissue of endometriosis appears to behave like the normally situated endometrium in response to hormonal stimulation. Complete atrophy and relief of symptoms are obtained by the use of androgens, but massive doses are required and virilization is therefore common. Moreover, the effects last only for as long as treatment is continued. Surgery remains for the present the treatment of choice.

Other suggested uses in women.—Although testosterone is in many respects a physiological opponent of œstradiol, it has in others a similar activity. Like the œstrogens, it is capable of inhibiting lactation, but it is less effective and is no longer used. It is also effective, although less so than the œstrogens, in relieving the symptoms of the climacteric, but is now used only in those cases in which the effective dose of one of the œstrogens produces an unwanted return of menstruation. Testosterone has also been used in cases of sterility, but no good effect has been established. It is at present the subject of experiments in the treatment of carcinoma of the breast, but although there is reason to think that its effects are mildly inhibitory, it is doubtful whether really practical results will be obtained.

Harmful effects in women.—The use of large doses of androgens for a sufficient length of time produces virilizing effects—acne, an increase in facial hair, deepening of the voice, and enlargement of the clitoris. The total dose required to produce these effects is very variable, some women being affected by comparatively small doses and others remaining unaffected by very large ones. I have the impression that virilization is less common during oral administration than during a course of injections. The disadvantage of implantation lies in the difficulty of discontinuing treatment should undesired symptoms arise. It is sometimes possible to remove an implanted pellet, but looking for it in a woman's subcutaneous tissues is like looking for a needle in a bottle of hay.

USES IN EITHER SEX

Influence on growth.—Concentration upon the growth factor of the anterior

pituitary, which at present is rarely of clinical value, has deflected attention from the fact that testosterone is a potent stimulus to growth of many tissues of the body, especially of the muscles, of the hair and, until the union of the epiphyses which it hastens, of the bones. The growth of normal experimental animals is accelerated, but so also is the union of the epiphyses, so that giants cannot be produced by this method. The most important clinical application of this knowledge is in the treatment of pituitary dwarfs. Although testosterone cannot replace the missing pituitary growth hormone or produce a normal skeleton, it can alleviate the condition, especially if used with thyroid extract.

Influence on body weight.—The male sex hormone causes the retention of nitrogen, water and sodium chloride. By this action it should theoretically be possible to minimize the negative nitrogen balance which occurs after severe trauma and major surgical operations. I am unaware of any controlled clinical experiments designed to test the truth of this suggestion, but clinical experience (a notably shaky foundation) suggests that it is sound. It is quite certain that testosterone is useful in those patients who have difficulty in regaining weight lost during illness and convalescence.

A good example is given by the case of a young man who, during military service in India, fell down a well and fractured a humerus, a radius, an ulnar and a femur. He lay at the bottom of the well, bleeding and unconscious, for many hours, and his condition on his arrival in hospital was critical. His recovery was stormy and his convalescence prolonged and complicated by Volkmann's contracture. His weight dropped from approximately 12 to 9 stone. A year or so after the cessation of treatment his weight had risen to only 10 stone and had been stationary for some months. He suffered from undue fatigue but from no other symptoms and the most careful investigation failed to reveal any cause for his leanness. Treatment with methyl testosterone restored his weight to normal in a few months and greatly increased his vigour.

Such treatment must, of course, be used with caution in women, owing to the risk of virilization, but no untoward results are likely to follow the use of methyl testosterone in a dosage of 5 mg. daily.

Frequency of micturition and enuresis.—Some of the early users of androgens in the treatment of fibroids observed that the frequency of micturition, especially at night, which is often so distressing a symptom, was quickly relieved. The improvement was usually ascribed to reduction in the size of the fibroid and the relief of pressure on the bladder, but it did not pass unnoticed that frequency was sometimes relieved without any obvious change in the size of the growth. It seems probable that the mechanism is similar to that which Hamilton and Gilbert postulated to explain the improvement in symptoms during the treatment of prostatic enlargement. I have on several occasions noted the disappearance of enuresis during the treatment of cryptorchidism with chorionic gonadotrophin, and have ascribed it to an increased endogenous production of testosterone. Methyl testosterone is apparently sometimes effective in controlling enuresis in boys, but I have not yet studied its use in this condition with sufficient care to conclude that the effect is specific.

Simmonds's disease.—In this condition androgens often produce remarkable improvement, the benefit presumably being derived from the anabolic effect of the hormones. The results are often so good that one is led to believe that the more important signs and symptoms of the disease are due to androgen deficiency.

Addison's disease.—Testosterone acts synergistically with deoxycortone in the treatment of this disease, and treatment by androgens reduces the necessary maintenance dosage of deoxycortone. Whether its benefits are due to simple substitution of a deficient steroid, or to sodium chloride retention, or to more subtle metabolic effects, is still not clear.

Cushing's disease.—According to Albright, many of the signs and symptoms of Cushing's disease are due to a strongly negative nitrogen balance which can be overcome by treatment with androgens. The hypothesis is of great theoretical interest but has not led to important practical results.

Peripheral vascular disorders.—Somewhat extensive claims have been made, especially in America, for the benefits of androgenic therapy in such conditions as Buerger's disease, Mönckeberg's sclerosis and Raynaud's disease. These claims are at present the subject of investigation by Dr. Warner Smith in my clinic at the Metropolitan Hospital. That testosterone is an effective vasodilator cannot be doubted and the results of treatment in some cases of intermittent claudication are highly satisfactory. In other cases they are negligible or absent, and we are not yet prepared to lay down any rules by which suitable cases can be selected. It was at first thought that the presence of extensive calcification of vessels would rule out the possibility of benefit, but further experience has shown that this is not the case. Nor can one be sure of improving the patient in whom no calcification can be detected. In the present state of knowledge it can only be said that the treatment is worthy of trial in every peripheral vascular disorder in which spasm plays a part, and that disappointment must be expected occasionally in the most seemingly hopeful cases. As no cure can be expected and treatment, if satisfactory, must be continued for a lifetime, implantation is obviously the best mode of administration. We are at present using 500 mg. doses.

Angina pectoris.—A similar rationale underlies the treatment by means of androgens of angina pectoris. In this condition also, some American reports have tended to be too optimistic, some authors claiming partial success in every patient treated. My own results in angina are similar to those in peripheral vascular disease: the occasional case responds satisfactorily, a few slightly, and many not at all. During treatment no changes are observed in the skiagram of the heart or in the electrocardiogram.

Other suggested uses in either sex.—Androgens have been administered in thyrotoxicosis, in the hope that they would exert an inhibitory action on the production of thyrotrophic hormone. The hope appears to be vain, for the basal metabolic rate is increased by androgenic treatment. Nevertheless, the

loss of weight in patients suffering from Graves's disease is sometimes stayed and an actual increase may occur, perhaps because of the general anabolic effects already mentioned. Because of this anabolic effect, androgenic treatment has been given to premature infants and good results have been claimed. Androgens are worthless in the treatment of hyperpiesis.

METHODS OF ADMINISTRATION

There is no justification for the administration of testicular extracts, which have no effect by mouth and negligible effects by injection. It is highly regrettable that they should still be on the market. They belong to that romantic stage of endocrinology at which men ate the testicles of their dead enemies in order to accumulate their procreative strength. In place of such extracts there are available the chemically pure testosterone and its compounds. In my own practice I use but three substances—testosterone by inunction or implantation, testosterone propionate by injection, and methyl testosterone by mouth.

Inunction.—In common with other hormones, testosterone produces its most powerful effects at the site of application. Although previously inunction was used in order to produce general effects without the bother of injection, this method is no longer used since the production on a commercial scale of orally active compounds. It still has its use when purely local effects are desired, as for instance in the treatment of fibro-adenosis of the breasts and in order to enlarge the clitoris. An average dose of testosterone by this route is 5 mg., two or three times a day.

Implantation.—The advantages of implantation are cheapness and freedom from trouble. Pellets of testosterone weighing 100 mg. are used. The dosage may lie between 100 and 1000 mg. according to the indications. Doses of more than 200 mg. are rarely used in women, for larger doses are not only unnecessary but carry a heavy risk of virilization. The operation takes about ten minutes and is performed in the consulting room or outpatient department under local anæsthesia. The effects last for about six months.

Intramuscular injection.—The propionate of testosterone is slowly absorbed from a muscular depot and injections need not be given more often than once a week. The effect is probably about ten times that of methyl testosterone by mouth. An average dose is 25 mg. weekly.

Oral administration.—Methyl testosterone is highly effective when swallowed and probably slightly more effective when absorbed slowly from the buccal cavity, in which circumstances it passes directly into the circulation without running the gauntlet of the liver. The usual range of dosage is 5 to 15 mg. daily. The advent of methyl testosterone tablets has largely superseded the use of intramuscular injections of testosterone propionate, although these are still useful in special cases.

REVISION CORNER

PENICILLIN IN THE TREATMENT OF INFECTIONS OF THE NOSE AND SINUSES

IN planning the treatment of *acute nasal infections* it is necessary to keep clearly in mind the stages in the development and resolution of these infections. Acute coryza is a virus infection, and obviously penicillin treatment cannot have any effect on its progress. It is believed, however, that the virus infection is merely the earliest stage of a "cold". The symptoms which give rise to the greatest discomfort are those due to the secondary infection by pathogenic organisms to which the virus infection affords the opportunity of invasion. Although the virus infection is unaffected by penicillin, the secondary infection can in many cases be expected to respond to penicillin treatment, provided the organisms causing the infection are penicillin sensitive.

LOCAL THERAPY

In all local treatment with penicillin two circumstances are essential: first there should be good access of the drug to the part containing the organism, and secondly, *the organism must be proved to be penicillin sensitive*. In acute coryza the congestion and oedema of the mucous membrane rapidly block the nose, rendering the effective application of any drug difficult, if not impossible. Therefore if penicillin is to be useful it must be used in the earliest stages while the nose is still open. If this condition is to be satisfied it is obviously impossible to wait for a bacteriological report before applying the drug, and therefore it must be used in a somewhat empirical fashion. To summarize, penicillin, to be effective, must be used in the earliest stages of the malady, before the onset of the symptoms caused by the invasion of the secondary infection, and before it is possible to obtain any information regarding the bacteriology of the condition.

Methods of administration.—There is a large number of methods of applying penicillin. It may be applied in the simpler methods as a snuff, as a spray, or as drops; or as aerosols, either in solution or powder. The latter are very fine mists or powder, which require specialized and expensive equipment for their application and cannot therefore be regarded as convenient methods for general practice unless there happens to be an outfit available.

Of the more easily used forms, sprays and drops have the disadvantage that ciliary action removes them so rapidly from the nasal mucous membrane that it is almost impossible to obtain and keep up a sufficient concentration of the drug to maintain bacteriostatic levels. As a *snuff*, however, by using a suitable vehicle, it is possible to retain the penicillin in the nose for longer periods. In a concentration of 500 to 1000 units per gramme of powder such a snuff will be found effective in many cases, if taken frequently—say, once every two hours. It must again be emphasized, however, that its use is limited, for it requires an informed patient to use it properly.

Immediate availability is essential and the patient must recognize the earliest symptoms, such as tickling of the soft palate, irritation of the nasopharynx, or the sensation of dryness in the nose. If the patient has to wait until next day to go to the doctor for a prescription and then take it to the chemist, it is probable that the time for use will have passed and disappointment will result. The greatest use for this type of treatment will probably be found in institutions and industrial undertakings where medical service is constantly available.

ACUTE SINUSITIS

Inflammatory reactions within the sinuses can be said to occur in most cases of acute coryza. Until there is obstruction either within the sinus itself or to the outflow of secretions, symptoms of headache, and the like, do not become manifest.

When an acute infection becomes obvious, intramuscular injection of penicillin is in all probability the most effective method of administration. Nevertheless, direct treatment can have some value and may be applied by direct injection into the affected sinus, or the penicillin can be introduced by displacement, i.e., by sucking air out of the sinuses and replacing it with penicillin solution as suggested by Proetz. In such cases treatment must be accompanied by instillation of ephedrine in saline to ensure sufficient shrinkage of the nasal mucous membrane.

It has been found that when the ostia of sinuses are patent it is possible to obtain sufficient concentration of penicillin within the sinuses by a somewhat similar procedure of alternate suction and pressure, using an aerosol mist. Treatment by this method has to be carried out several times daily and requires the special equipment already referred to.

CHRONIC NASAL DISEASE

In general, it may be said that the local use of penicillin in chronic nasal disease is rarely effective. One of the chief reasons for this is the frequency with which there is an associated allergy. In such circumstances there can be nothing but a transient effect, even when sensitive organisms exist.

Occasionally some effect may be obtained in chronic nasal congestion by the use of drops (5,000 to 10,000 units per ml.). When this is tried, the patient should be in the supine position with head fully extended and should remain in this position for some minutes. The treatment should be repeated every four hours. If nasal congestion is marked, this procedure should be combined with instillation of ephedrine and saline drops to give the penicillin access to every part of the nose. If this form of treatment is not practicable the penicillin may be given as a spray, but in the majority of cases it has proved ineffective.

In *chronic sinusitis* the same principles hold good. When there is allergy, or marked oedema, or polyposis of the mucous membrane, penicillin will almost certainly fail, but when antral washouts show the presence of penicillin-sensitive organisms, then the introduction of penicillin either by puncture, displacement, or aerosols, will in most cases give good results.

SIDE-EFFECTS

A word should be said about reactions to penicillin. These must be expected in a small proportion of cases, and may consist of urticaria or dermatitis of the nasal vestibule. This responds to the usual remedies and the withdrawal of the penicillin. Another form of idiosyncrasy which has been encountered is oedema of the soft palate and the fauces. This is extremely uncomfortable and, if not recognized early, takes a considerable time to clear up and leaves a sensitiveness of the mucous membrane of the mouth even after the oedema has subsided.

CONCLUSION

The advice given can be summarized by saying that penicillin treatment of acute infections of the nose does not lend itself to scientific control such as is desirable with this drug. To be effective, it must be used in the earliest stages. The best results are obtained with special apparatus, whilst of the simpler forms, a snuff is probably the most useful. In general, results of local nasal treatment, except in certain specially favourable circumstances, have been disappointing.

I. SIMSON HALL, M.B., F.R.C.P.ED., F.R.C.S.ED.

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ness, head retraction, twitchings and convulsions may develop and indicate kernicterus—the most serious complication, in which the basal nuclei are destroyed. Kernicterus is often fatal in the acute stage. The survivors are spastic, mentally defective, or have choreo-athetosis.

Confirmation of the diagnosis is by serological tests and finding antibody in the mother's blood; in many cases the diagnosis is made in the antenatal clinic by routine Rh grouping of mothers at their first attendance and examination of serum for antibody late in pregnancy; when this is found it is wise to arrange for delivery in hospital.

Treatment consists in blood transfusion with Rh-negative blood; this may have to be repeated several times in the neonatal period. Replacement transfusion, in which the baby's blood is replaced with Rh-negative blood, is being done in certain centres; the umbilical vein is used for the transfusion, which must be done within eighteen hours of birth. Whether this latest method of treatment prevents kernicterus is not yet known; simple transfusion does not.

Acholic jaundice.—This occurs rarely in the neonatal period. It has the usual features of a hæmolytic jaundice. Other babies in the family are not affected. The diagnosis is made by excluding icterus gravis and by finding increased red cell fragility in the baby itself or in the parents or siblings in whom the disease, which is usually familial, may be latent. Blood transfusions may be required for the anaemia. Splenectomy affects a complete cure but should be delayed until the end of the first year. Kernicterus does not occur.

OBSTRUCTIVE JAUNDICE

Congenital obliteration of the bile ducts.—Characteristic features are progressive jaundice, clay-coloured stools, and very dark urine containing bile salts and pigments. There is no anaemia. The pathology is often obscure: there may be a developmental abnormality or a prenatal obliterative cholangitis; there is always secondary cirrhosis of the liver.

The onset of jaundice occurs during the second or third week with few symptoms except failure to thrive. The liver becomes enlarged and hard, the spleen enlarges secondarily. Only rarely is the obstruction amenable to surgery; when it is not, the disease is always fatal.

TOXI-INFECTIVE JAUNDICE

In this group the liver is primarily at fault; it is enlarged and may be tender. The stools are normal in colour; the urine contains bile.

Syphilis.—The baby may be jaundiced at birth; more often the onset is in the second or third week. Other signs of syphilis are always present. The diagnosis is confirmed by finding a positive Wassermann reaction in the mother's blood. Neonatal syphilitic jaundice is evidence of a severe infection and the prognosis is poor even with antisyphilitic treatment. Fortunately, since the routine use of Wassermann reactions antenatally and treatment of syphilitic mothers during pregnancy, syphilitic jaundice is rare.

Sepsis.—Jaundice may occur as a complication of any severe sepsis in the neonatal period, but commonly in umbilical sepsis, septicaemia or pyæmia, and gastro-enteritis. Usually the clinical picture is dominated by the signs and symptoms of infection, jaundice being but an incident which, however, carries a grave prognosis. The treatment is that of the causal infection: penicillin and sulphonamides should both be given in full doses with supportive measures, such as intravenous saline. Blood transfusions are often required. In severe infections with pyogenic organisms, notably streptococci and *B. coli*, there is often a hæmolytic process at work, so that the jaundice may be due in part to liver damage and in part to excessive blood destruction.

JAUNDICE IN THE NEW-BORN BABY

JAUNDICE is such a common symptom in the new-born infant that it only arouses suspicion when there are unusual concomitants. It has been said that "the symptom icterus is not as frequent in any other period of life as in the first week and—a matter of particular importance—hardly ever as harmless"; this statement is true because all forms of jaundice except "physiological" jaundice of the newborn are rare, but they have a grave prognosis.

PHYSIOLOGICAL JAUNDICE OF THE NEWBORN

This shows itself between the second and fifth days, commonly fades in a week, but may last for four weeks. It occurs in about 50 per cent. of infants, and the smaller the baby the more likely it is to become jaundiced. There are two factors in the production of physiological jaundice—blood destruction and immaturity of the liver. At birth the infant is polycythæmic; when pulmonary respiration is established the excess red cells are unnecessary and are destroyed; this occurs in all new-born infants. The variable factor is the adequacy of the infant's liver in excreting excess blood pigment; hence the degree of jaundice may, in a sense, be taken as a measure of the immaturity of the liver.

Physiological jaundice causes no symptoms beyond slight lethargy and reluctance over feeds when marked; the stools are normal in colour, the urine rather dark from excess urobilin. There are no complications and no treatment is required.

PATHOLOGICAL JAUNDICE

Pathological jaundice may be classified into:—

- (1) Hæmolytic jaundice.
 - (a) Icterus gravis neonatorum.
 - (b) Acholuric jaundice.
- (2) Obstructive jaundice.

Congenital obliteration of the bile ducts.
- (3) Toxi-infective jaundice.
 - (a) Syphilis.
 - (b) Sepsis.

HÆMOLYTIC JAUNDICE

Excessive blood destruction is the basis of this type of jaundice; it follows that anæmia is always present and evidence of active red blood cell regeneration. The spleen and liver are always enlarged, the stools are normal in colour and the urine is dark, due to excess urobilin excretion, but does not contain bile salts or pigment.

Icterus gravis neonatorum.—This, the most common hæmolytic anæmia of the newborn, is due to Rhesus incompatibility between mother and fœtus. These babies are Rhesus positive, their mothers Rhesus negative. During pregnancy the mother becomes sensitized to the Rhesus factor and produces an antibody which agglutinates and destroys Rhesus-positive red blood corpuscles. Red cell destruction occurs already during the later months of pregnancy so that the cord blood taken at the moment of birth shows anæmia. The first baby escapes the disease, but subsequent Rhesus-positive fœtuses are all affected. Fortunately only a small proportion of Rhesus-negative mothers have this faculty of forming antibody during pregnancy, so that the disease is less common than might be expected.

The affected baby, then, will not be a first baby; there may be a history of still-births or babies with anæmia, jaundice or both. The diagnosis is suspected when jaundice is present at birth or appears within forty-eight hours, and there is an associated anæmia with a palpable spleen. At first the baby is not ill, but soon becomes lethargic and sucks poorly, whilst in severe cases there may be purpuric hæmorrhages and death from anæmia. Cerebral signs, such as a shrill cry, restless-

tissue that is sensitive to the action of oestrogens when artificially administered. The most successful result with endocrines can of course produce only one type of breast; thus it is felt that this charming lady would be better advised to resort to the art of her dressmaker rather than to rely on endocrine preparations that are uncertain and unsympathetic to the vagaries of fashion.

J. S. RICHARDSON, M.V.O., M.D., F.R.C.P.

Undescended Testicle and Malignancy

QUERY.—Is any treatment indicated for a man aged twenty-nine found at a routine examination to have one undescended testicle, not palpable in the inguinal canal or elsewhere and presumably intra-abdominal? The other testicle is normal and in the scrotum; sexual function is normal. It is commonly stated that undescended testicles are more liable to develop malignant neoplasms than normal testicles. Is there any reliable evidence for this, and is surgical removal justified for this reason alone?

REPLY.—Statistics strongly support the view that malignant disease is much more common in the undescended than in the descended testicle. The percentage of cases of undescended testicle in the male population is about 0.2 per cent. If failure to descend was not associated with an increased risk, the incidence of malignancy among undescended testicles would be the same. But it is actually found to be about fifty times more frequent. Dean found it in 13.5 per cent. of his series; Miyagi in 12.4 per cent., and Gordon Taylor in no less than 30 per cent. Pace and Cabot cut sections of undescended testicles that they had removed from patients between the ages of eighteen and sixty-seven; and they found unsuspected early malignant disease in two, and possibly three, out of the twenty-four specimens examined. I would therefore advise surgical removal of a misplaced testicle merely as a safeguard against malignant changes.

KENNETH WALKER, F.R.C.S.

Sore, Dry Mouth

QUERY.—I should be grateful for any suggestion you can give me to help a patient of mine with a very sore, dry mouth. She is aged fifty-seven, and first noticed a little trouble three years ago. She now has a red, raw tongue with flattened papillae, a general reddening of the buccal mucous membrane, and sore angles of the mouth (? perleche or cheilosis). The complaints are of intense soreness and burning (like "red hot pepper"), and extreme dryness aggravated by talking—she specifies a dryness requiring

moistening and *not* a thirst. Eating solid food is almost impossible. Last year she had a coronary thrombosis. Later investigation showed achlorhydria, with aching limbs (? paronychia rather than myositis); a tentative diagnosis of subacute combined degeneration of the cord was made. Her Hb. was 70 per cent. colour index, 0.8. In January 1949, carcinoma of the caecum was discovered and excised. The patient has a good deal of worry apart from all this. She has had prolonged treatment with injections of crude liver and riboflavin, acid mixtures and tablets, vitamin C, riboflavin and becosym by mouth, and iron (Hb. since operation 90 per cent.). She is now having a prophylactic course of Htr. Her dentures are comfortable and have been in for five to six years. Bowel movement regular with laxatives; appetite good but food refused. Urine—no abnormal constituents.

REPLY.—Although achlorhydria is not uncommonly associated with buccal mucosal atrophy and soreness, it is unlikely that such a connexion exists in this case. The sore mouth of pernicious anaemia or of achlorhydric microcytic anaemia presents a smooth pale tongue, although here and there inflamed fissures may be seen. Extreme dryness is not a feature of "anaemic stomatitis". In any case the treatment given has been ineffective. The report suggests to me that she may have atrophy of the parotids. This is seen in women of this age and may be suspected if the face is sunken over the glands. A sialogram is diagnostic. An alternative is post-menopausal atrophy and soreness. Usually, however, the signs are slight and those of atrophy only. Stilbæstrol, 1 mg. daily, will effect improvement within a month.

A. H. DOUTHWAITE, M.D., F.R.C.P.

Jaundice and Rheumatism

QUERY.—I have recently read in an article written by a doctor in a lay journal that "a man or woman who has rheumatism and then contracts jaundice is usually free from rheumatism for a long time afterwards". Is this the case, and if so, what is the rationale?

REPLY.—The ameliorating effect of jaundice in rheumatoid arthritis was first emphasized some years ago by Hench of the Mayo Clinic, and has been observed by other investigators. There seems to be no question about the fact, but the mechanism by which the beneficial effect is accomplished has not been recognized. Effort has been made to produce jaundice artificially, particularly by the injection of bile salts, but this has not been successful in producing relief of the rheumatic symptoms.

ROBERT M. STECHER, M.D.

NOTES AND QUERIES

Treatment of Chronic Ulcerative Colitis

QUERY.—A female patient, aged twenty-five, is suffering from ulcerative colitis. No specific organisms have been discovered. These attacks have been coming on during the past five years. Last year she had two attacks both lasting approximately three months. During the attack there is loss of weight, free rectal bleeding and loose stools. Stools may be as many as twenty per day. She has had treatment with sulphaguanidine, penicillin, vitamin B₁, phenobarbitone, morphine and chlorodyne orally, and starch and opium retention enemas. All have been tried for long periods, and at present she is taking paraveston (Allen & Hanburys). The end-result appears to be that she clears up for a time with or without treatment. Surgery has not been considered. Is there any further line of medical treatment indicated in this case?

REPLY.—New forms of treatment for ulcerative colitis are notoriously difficult to assess; the patient is so often readily influenced by new remedies and there is a natural tendency for remissions to occur, as in this case. However, since the cause of the disease is unknown, we cannot afford not to try new lines of treatment empirically, combined of course with the usual general measures—low-residue diet, vitamin supplements, sedatives, and blood transfusions. Successes have followed the use of the sulphonomides, and phthalylsulphathiazole, 2 g. four-hourly by day for one month, is superior to sulphaguanidine. Parenteral penicillin, 1 million units daily, combined with this course of oral phthalylsulphathiazole, has given some good results. Streptomycin, 3 g. daily by mouth for three weeks, has proved effective in some cases in America, where newer antibiotics, for instance oral bacitracin, are being tried at the present time. Methyl thiouracil, 0.6 g. daily for four weeks, has been found effective in some cases, producing rapid relief of symptoms in about a week. Its mode of action is not known but there may be some significance in the fact that it is chemically similar to thymine, which is effective in the treatment of some cases of tropical sprue.

Miller of Philadelphia conducted an interesting experiment in which a Miller-Abbott tube was passed down to the ileo-cæcal valve, where it was left for several weeks during which continuous suction was maintained. In this way all the intestinal contents were removed before they could enter the colon, and the effect of an ileostomy was reproduced. Several patients

responded well to this temporary measure. Finally, I would suggest that in a case of such chronicity surgery must be considered. Resting the large bowel by means of an ileostomy is a dependable measure provided it is done while the patient is still fit to undergo the operation. Most patients gain weight rapidly and are able to lead active lives. The disadvantages of the stoma are small compared with the symptoms of the chronic disease in which at the present time permanent and complete cures are uncommon.

LIEUT.-COLONEL W. H. HARGREAVES, O.B.E.,
M.R.C.P.

Endocrine Therapy for Enlargement of Breasts

QUERY.—An elegant woman patient consulted me, aged thirty-two years. She is married and has three children, with some two years between each child. The youngest child is now two and a half years' old. Her general health is good. She noticed that her "figure", that is her bust, dwindled more and more with each confinement. Now she is flat-chested and regrets, if not resents, her loss; for she has charm. Can any treatment be established that is promiseful of success in the restoration of her previous figure? I am aware of injections such as antuitrin-S, intermittent ovarian follicular and corpus luteal therapy, and of local applications, to wit, anointing with, say, menformon. But I wish not to put my patient to expense and needless treatment without a fair chance of success.

REPLY.—The most hopeful form of endocrine therapy in a case like this is the local application of synthetic or natural oestrogens in an ointment. Dienoestrol, in the strength of 2½ per cent., is a suitable preparation: half a gramme of the ointment should be rubbed into each breast daily for the first eighteen days of the menstrual cycle. This treatment should be pursued for at least four months if it is to be given a fair trial. It is feared, however, that it is likely to be successful in only a minority of cases, and in them the increase in the size of the breasts will be only moderate, so that anything like the development of a "Bronzino Venus" will not be achieved. This patient's breasts have become progressively smaller after each of three pregnancies. Since she has had these pregnancies she has not had a series of severe depressions of the whole function of the anterior pituitary gland, but rather a failure of the breast tissue to react to normal endocrine influences after the great stimulation associated with pregnancy has ceased. She is therefore unlikely to have breast

Emotional upset, worry or excitement, or a prolonged stay in the dark may precede the onset of symptoms. In the summary to his article the author gives a list of diagnostic points—“(1) If an eye with inflammation of the uveal tract develops increased redness, pain, visual disability and steamy cornea, glaucoma should be suspected. (2) If an ocular injury is followed by congestion, pain, blurred vision, or steamy cornea, the possibility of increased intra-ocular pressure must be considered. (3) If an individual with cataract suddenly develops ocular pain, secondary glaucoma has probably supervened. (4) Unbearable pain following central vein occlusion means glaucoma. (5) If an infant has one large eye or different sized large eyes with deep anterior chambers and corneal streaks, particularly if the cornea is steamy, glaucoma is present. (6) Sudden intense pain with marked loss of vision, steamy cornea, dilated pupil, and nausea or vomiting indicate acute primary glaucoma”. Finally, the author stresses the fact that mildness of symptoms should not offer any sense of security: “Beware of intermittent blurring of vision, halos around lights, dull headache or eyecache, especially in the morning, after a stay in the dark, or after excitement”. It is also necessary to beware the need for frequent changes of glasses, dilated sluggish pupils, and shallow anterior chamber.

Avoidance of Complications of Dental Extractions

“THE importance of preventing inhalation of fragments of dental tissue during extractions under nitrous oxide or other general anæsthetic is now generally realized” writes J. Hallam (*British Dental Journal* April 14, 1949, 86, 205), and he continues: “Equally important, but not so widely appreciated, is the fact that infected blood and fluid elements are as often, or possibly more often, responsible for the onset of lung infections”. As an adjunct to the usual methods of controlling blood during the extraction of teeth, the author has devised a sucker to be attached to the saliva ejector tube which, in the hands of a skilled assistant, is stated to remove the bulk of blood from the mouth, thus permitting the mouth pack to be removed practically dry after the extraction. The sucker is silver plated and can be sterilized by boiling, and is easily cleaned, if necessary with the help of a Higginson's syringe. The following points are stressed as aids to avoidance of pneumonitis and other sequelæ—“(1) Extract early in the day. (2) Do not extract an excessive number of teeth at any time (3) Leave the pack in until the patient is round from the anæsthetic

If in spite of the use of the sucker it is heavily blood stained, remove it and replace it with a fresh one. (4) Use postoperative hypnotics and hypo-analgesics with extreme caution . . . (5) If a patient retires to bed after extractions, it is helpful to raise the foot of the bed . . . and allow only one pillow. (6) If, in spite of these precautions, it is suspected that infected material has in fact been inhaled, make full prophylactic use of antibiotics and chemotherapy”.

Picrotoxin in Barbiturate Poisoning

ACCORDING to E. A. Newman and M. Feldman, Jun. (*Archives of Internal Medicine*, May 1948, 81, 690), severe barbiturate poisoning may require larger doses of picrotoxin than those usually recommended: “While a patient is comatose, there is no toxic dose of picrotoxin until a preconvulsive state is reached”. In a series of eleven severe cases the average dose administered during the acute phase was 15 mg. every fifteen minutes. Amounts ranging from 9 to 45 mg. per dose, given intravenously, were necessary at fifteen-minute intervals. As improvement set in, the dose was progressively reduced. Once muscular twitching was obtained, the dose was adjusted so as to maintain “constant irritability or twitching just below the convulsive threshold”. This resulted in “many of the patients” having “short convulsions”. In several patients amphetamine was given to stimulate the cerebral cortex, thus supplementing the action of picrotoxin which is mainly on the lower brain centres. One of the patients in the series received a total of 14,196 mg. of picrotoxin, whilst another received 5,139 mg. Other essential constituents of treatment in such cases include “maintenance of fluid balance, constant vigilance in keeping the air passages clear and, above all, immediate administration of antibiotic substances to help prevent pulmonary infection”.

Undecylenic Acid in Psoriasis and Neurodermatitis

A PRELIMINARY report on the use of undecylenic acid in the treatment of psoriasis and neurodermatitis is given by H. H. Perlman (*Journal of the American Medical Association*, February 12, 1949, 139, 444). The drug was administered orally in dosage of 7.5 g. daily, in divided doses, after or before meals, and gradually increased to 10 to 15 g. daily in divided doses. The effective daily dosage for average adults seemed to be 10 g. daily: no harmful effects occurred with this dosage, nor was there any gastro-intestinal disturbance. The patients with chronic psoriasis (17) showed definite improvement: dis-

PRACTICAL NOTES

Penicillin and Ice Therapy

THREE groups of patients with infected varicose ulcers, infected epidermophytoses, and infected wounds of the extremities have been treated with ice applications, alone and in conjunction with penicillin, and penicillin alone. The results are recorded by R. A. Gilbert, R. A. Call, and D. J. Roose (*Bulletin of the Johns Hopkins Hospital*, March 1949, 84, 245). The first group comprised fifteen cases of infected varicose ulcers of the leg. Five patients were treated with local application of ice bags for five days, and on the tenth day, as symptoms recurred, penicillin was necessary to complete cure. Five patients received penicillin alone: 50,000 units intragluteally, every three hours to a total of 1.2 to 1.6 million units. In the five remaining cases ice was placed around the ulcer for one hour; the area was then prepared with tincture of merthiolate, and 500,000 units of penicillin, dissolved in 10 ml. of 1 per cent. novocain, were infiltrated at the site of the ulcer. Ice bags were kept around the ulcers for five days. The average hospitalization times of the three sub-groups were thirty-eight, twenty-five and twenty days respectively. The second group treated consisted of fifteen cases of secondarily infected epidermophytosis of the leg, subdivided into three sub-groups as in group 1, and treated on the same lines, except that in the first sub-group no penicillin was needed to complete the cure, and in the second sub-group the dosage of penicillin was 30,000 units three-hourly for a total of 240,000 units. The hospitalization times in this group were twelve, eight and five days respectively. Group III comprised twenty patients with infected wounds, and the average hospitalization times for the three sub-groups, i.e. ice alone, penicillin alone, and ice and penicillin, were eleven, eleven and six days. It is claimed that ice-penicillin therapy proved "decidedly superior therapeutically to either interrupted intragluteal penicillin or ice", the advantages being: (1) shorter hospitalization; (2) more rapid disappearance of signs and symptoms of infection; (3) lower total dosage of penicillin to effect cure, and (4) disappearance of pain on chilling.

Treatment of Polycythæmia Vera

WHAT is claimed to be the second case of polycythæmia treated by artificial infestation with *Ancylostoma duodenale* is reported from Cairo by H. F. Nagaty and A. F. Zanaty (*Transactions of the Royal Society of Tropical Medicine and Hygiene*, March 1949, 42, 493).

The infestation was produced by making a culture from the stools of a patient with ancylostomiasis, and applying 150 to 250 larvæ to the back end abdomen. The drops of water containing the larvæ were spread over as large an area as possible so as to allow quick evaporation and penetration. Four applications in all were made, and after the first two the patient complained of dermatitis, tracheitis and diarrhæa. These symptoms were attributed to migratory stages of the larvæ and were taken to indicate the success of the infection. The original blood count was: 8,000,000 red blood cells per c.mm., and 140 per cent. hæmoglobin. The final figures were: red blood cells, 5,000,000 per c.mm.; hæmoglobin 60 per cent. The advantages claimed for this method of treatment include:—(a) *Ancylostoma* infection can easily be produced in tropical and subtropical countries. (b) One or two infections may last for a long time, and ancylostoma anemia does not recover spontaneously. (c) *Ancylostoma* infection produces no lasting complications in adults and does not require skilled supervision. (d) Even after complete elimination of the infection the anemia remains more or less stationary. (e) The parasites can easily be removed if any untoward symptom develops.

Diagnosis of Glaucoma

"THERE are approximately 200,000 blind persons in this country. Over 20,000 of these are blind from glaucoma"—writes J. A. Inciardi (*New York State Journal of Medicine*, April 1, 49, 836), who stresses the importance of early diagnosis and treatment for the prevention of blindness. A typical attack of primary glaucoma is 'easy to diagnose: the sudden onset with intense pain in the eye and head, nausea, vomiting, marked reduction of vision, redness of the eye and eyelid, the eyeball tender and very hard to the touch, the cornea steamy, pupil dilated, and fundus not visible, is more liable to occur in the early morning after an emotional upset, a stay in the dark or the use of a drug for dilatation of the pupil. The most common, and the most disabling type is chronic simple glaucoma: the onset is slow and insidious, and the condition often reaches an advanced stage before the patient is aware that anything is wrong. The earlier symptoms are chiefly pressure effects causing hazy vision and the appearance of rainbow coloured halos around lights. The pressure on the nerve endings may cause eye pain or headache, and interfere with motor function, focusing power, and power to adapt in the dark.

Emotional upset, worry or excitement, or a prolonged stay in the dark may precede the onset of symptoms. In the summary to his article the author gives a list of diagnostic points:—“(1) If an eye with inflammation of the uveal tract develops increased redness, pain, visual disability and steamy cornea, glaucoma should be suspected. (2) If an ocular injury is followed by congestion, pain, blurred vision, or steamy cornea, the possibility of increased intra-ocular pressure must be considered. (3) If an individual with cataract suddenly develops ocular pain, secondary glaucoma has probably supervened. (4) Unbearable pain following central vein occlusion means glaucoma. (5) If an infant has one large eye or different sized large eyes with deep anterior chambers and corneal streaks, particularly if the cornea is steamy, glaucoma is present. (6) Sudden intense pain with marked loss of vision, steamy cornea, dilated pupil, and nausea or vomiting indicate acute primary glaucoma”. Finally, the author stresses the fact that mildness of symptoms should not offer any sense of security: “Beware of intermittent blurring of vision, halos around lights, dull headache or eyeache, especially in the morning, after a stay in the dark, or after excitement”. It is also necessary to beware the need for frequent changes of glasses, dilated sluggish pupils, and shallow anterior chamber.

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appearance of the lesions, relief of itching, and disappearance or improvement of joint pains. A group of 8 patients with neurodermatitis showed improvement or disappearance of lesions and itching. Side-effects of the drug included nausea, vomiting, burning sensation in the epigastrium, and diarrhoea. As many patients complained of a bitter or unpleasant taste in the mouth, it is stated that the stomach distress and nausea could probably be eliminated by the use of enteric-coated pills. Other symptoms apparently to be attributed to the drug were folliculitis, frequency of micturition, headache, conjunctivitis, and axillary adenitis. In conclusion it is stated that although "definite claims for undecylenic acid cannot be made from the comparatively small number of patients studied . . . undecylenic acid seems to hold a great deal of promise in the improvement and possible prevention of recurrences of psoriasis and neurodermatitis".

Brilliant Green for Chronic Ulcers of the Skin

BRILLIANT green, a derivative of triphenylmethane, is recommended by A. W. Feldberg (*New England Journal of Medicine*, October 21, 1948, 239, 613) for the treatment of chronic ulcers of the skin. The dye was used as a 2 per cent. solution in distilled water. The technique adopted was that the ulcer was first thoroughly cleaned with hydrogen peroxide and alcohol. The dye was then painted on daily until healing was progressing well—usually seven to ten days. It was then applied on alternate days until healing was complete. After each treatment the ulcer was covered with a dry sterile dressing. Although his report is based upon only about twenty cases, the author believes that brilliant green possesses many advantages over other forms of treatment. Among these advantages he includes: its bacterial action, its stimulating effect on epithelium and granulation tissue, its lack of toxicity, its cheapness and the ease of application. It has been reported previously that aqueous solutions of brilliant green are not stable, but in this investigation it was found that "stock aqueous solutions continued to give excellent clinical results months after their preparation".

Radiological Diagnosis of Roundworms

IN reporting a case in which the presence of ascaris in the bowel was demonstrated by X-rays, C. Strang and C. K. Warwick (*British Journal of Radiology*, November, 1948, 21, 575), draw attention to the fact that radiology

is seldom required for this purpose. On the other hand, routine radiological examination of the gastro-intestinal tract may demonstrate the presence of unsuspected ascaris infestation. In addition, there are occasional cases in which eggs may be absent from the stools even though roundworms (either males or immature females) are present in the gut. A recent American report is quoted in which in a series of one hundred cases undergoing barium examination of the small intestine, ascaris infection was demonstrated in six cases, in none of which had their presence been suspected clinically. The radiological signs of ascaris infection are: (1) sharply defined band-shaped filling defects; (2) linear shadows due to adherence of the barium to the exterior of the worm; (3) thread-like shadows caused by the presence of barium in the enteric canal of the worm; (4) evidence of disordered motility of the gut.

The Benzidine Occult Blood Test

THE use of the benzidine test for determination of occult blood in the faeces in patients undergoing treatment with iron for anaemia due to gastro-intestinal haemorrhage is described by H. W. Linn (*Medical Journal of Australia*, January 1, 1949, 36, 15). The technique of the test is as follows: "A portion of faeces, the size of a marble, is emulsified in 10 millilitres of water and boiled for a few minutes. The emulsion is filtered drop by drop into a test tube containing equal parts of hydrogen peroxide and a freshly prepared saturated solution of benzidine in glacial acetic acid. A deep blue colour developing within a few minutes indicates the presence of blood". A meat-free diet for three days is all the preparation required for the test. The result of the test was not influenced by the administration of iron or of meat extracts. In all experimental groups, consisting of twenty-five cases in all, negative results were obtained, but in a control group of twenty-one patients who had meat-free diet for three days, one positive result was obtained, and in a further control group of twenty patients receiving high meat content diet there were five positive results. Using the method described, positive results were obtained with less than 0.01 millilitre of blood.

Optic Neuritis due to Digitoxin

WHAT is claimed to be only the second case recorded of retrobulbar optic neuritis due to digitoxin intoxication is reported by P. Sykowski (*American Journal of Ophthalmology*, April 1949, 32, 572).

A male, aged forty-seven, had been taking digitoxin for four weeks on account of heart failure: 0.2 mg. thrice daily for one week and then twice daily. During the third week

of treatment vision suddenly became blurred. There was no nausea or vomiting. Examination revealed uncorrected visual acuity of 20/200 in the right eye and 20/200-1 in the left eye, corrected vision being 20/100-2 in the right eye and 20/100-1 in the left. There was mydriasis, sluggish reaction to light, and pericentral scotomas.

Treatment consisted of thiamine chloride, 20 mg. thrice daily, but it was felt that it was not safe to reduce the dose of digitoxin immediately. After ten days digitoxin was reduced to 0.2 mg. daily and four days later vision began to improve. By the ninth week corrected vision in both eyes was 20/25 and the scotomas were much smaller. While on the reduced dosage of digitoxin the patient reported that there was no "smokiness" of his vision on rising in the morning, but that it recurred to a certain extent after taking his tablet of digitoxin, and during a three-day period when he took no digitoxin he reported complete absence of "smokiness". It is stated that digitoxin has a selective affinity for the papillomacular bundle. Attention is drawn to the fact that, compared with digitalis, digitoxin is almost completely absorbed and produces no gastric irritation. A central scotoma may therefore be an early sign of digitoxin poisoning.

Right-Handed or Left-Handed?

In a review of "handedness", R. S. Eustis (*New England Journal of Medicine*, February 17, 1949, 240, 249) points out that at the present time approximately 95 per cent. of the adult civilized world is right-handed. There has been a steady diminution in left-handedness throughout the ages: about 50 per cent. of stone-age implements were made for left-handed use, compared with only about 25 per cent. of bronze-age implements. There is a similar diminution in left-handedness with age: 20 per cent. of kindergarten children, 10 per cent. of school children, and only 5 per cent. of adults. Both environment and heredity probably play a rôle in the production of left-handedness. It is also suggested that "there is some relation between a tendency toward ambidexterity and comparative weakness in the use of language". Left-handedness and ambidexterity are both said to be more common among children, the mentally retarded, criminals and geniuses. The explanation in the case of the last is that "geniuses by and large are extremely individualistic and hence more likely to resist successfully the external pressures toward right-handedness". It is considered that the chances of producing stuttering by teaching an apparently left-handed child to write with the right hand have been exaggerated. All such children should be so taught when writing begins because "the use of the right hand fits in better with the left-to-right direction of writing

and also because it conforms to the custom of the majority and hence is easier psychologically". Only if signs of nervous strain develop, such as stuttering, should the attempt be given up. In teaching the child who is to use his left hand, it is important that the paper should be properly placed, i.e., slanted with the top border to the right. Such children should also be allowed to write with a slight backhand slant, if they so prefer.

Local Injection of Penicillin in Carbuncles

A SERIES of twenty cases of carbuncle, three of which were diabetic, have been treated by local infiltration of penicillin by T. H. Bate (*Annals of Surgery*, April 1949, 129, 494). The method employed was as follows:—A solution of penicillin-novocain was employed, 100,000 units of penicillin per ml. of 2 per cent. novocain. The solution must be mixed just before using. The skin surrounding the carbuncle is carefully cleaned just beyond the indurated area. Then, using a fine hypodermic needle (24 to 26 gauge) and a lock-type syringe, a small wheal is made in the skin (it is stated that considerable pressure is required for infiltration in this area) and the needle is then carried into the deeper tissues where the solution may be injected with greater ease. The entire area of the carbuncle is surrounded, using from three to five points of injection. It is emphasized that the solution is not injected into the carbuncle, but around it, beyond the indurated zone. As a rule 5 to 20 ml. of the mixture is sufficient. Hot packs are recommended and the patient is seen daily. Of the cases treated, in ten the carbuncle was on the neck, in four on the lip, in three on the hand, in one on the thigh, one on the buttock, and one on the abdomen. Usually there is no tenderness at the site of injection, and it was not found necessary to anesthetize any of the patients treated. After the injection the carbuncle shows pus exuding from the small openings; on the second day drainage is usually profuse, and persists for two or three days, according to the size of the carbuncle. Healthy granulation occurs and epithelization is rapid, the resulting scar being thin and white and non-adherent to the skin. Usually the induration subsides and disappears within two to four weeks. In the treated series there were no deaths, and no recurrence of the infection locally. The average hospitalization period was three days, and the time lost from work 8.6 days. It is stated that the method can be used at any stage of the disease: it is simple, and the relief from pain is immediate.

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